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(54) Title: PHOTOACTIVATABLE COMPOUNDS FOR THE PREVENTION OF INTIMAL HYPERPLASIA AND OTHER DISEASES			
(57) Abstract			
<p>A broad class of photosensitive compounds having enhanced <i>in vivo</i> target tissue selectivity and versatility in photodynamic therapy. Many furocoumarin compounds, such as psoralens, exhibit cytostatic activity when photoactivated but exhibit little <i>in vivo</i> specificity for selectively accumulating in any particular target tissue such as atherosomatous plaques. Reactive Oxygen Producing Photosensitizers ("ROPPs") are photoactivatable compounds having an affinity for hyperproliferating cells (such as atherosomatous plaque cells), which when photoactivated, produce cytotoxic reaction products. The photoactivity of a ROPP, such as a porphyrin, may be reduced by metalating the porphyrin while the selective affinity of the metalized ROPP for hyperproliferating tissue remains substantially unchanged. By linking a furocoumarin compound to a ROPP to form a F-ROPP, the cytostatic properties of the furocoumarin portion of the F-ROPP can be exploited while the selective affinity of the ROPP portion of the compound for hyperproliferating cells such as atherosomatous plaque provides enhanced tissue selectivity without cytotoxicity. <i>In vivo</i>, certain F-ROPPs may be forced to selectively accumulate in a target tissue by illuminating only the target tissue with light having a wavelength operable for photoactivating the F portion of the F-ROPP thereby causing the F-ROPP to either form a monoadduct with or cross-link the cellular DNA in the target tissue. Light of a second wavelength can then be delivered to the target tissue to photoactivate the ROPP portion causing further interference with cellular activity.</p>			

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**PHOTOACTIVATABLE COMPOUNDS FOR THE PREVENTION OF INTIMAL  
HYPERPLASIA AND OTHER DISEASES**

1                   **BACKGROUND OF THE INVENTION**

2                   1.     Field of the Invention

3                 This invention relates to photoactivatable compounds and to methods for using  
4                 the compounds for diagnosing and treating medical conditions.

5                   2.     Prior Art

6                 Photodynamic Therapy (PDT) is used for treating various diseases including  
7                 cancer, psoriasis, vascular disease, non-cancerous hyperplastic disease such as benign  
8                 prostatic hyperplasia, macular degeneration, glaucoma, and certain viral infections.  
9                 PDT requires concentrating a photosensitizer drug in a target tissue then  
10                photoactivating the compound with a device which includes a light source providing  
11                light at a particular wavelength and power level. The drugs administered for PDT are  
12                commonly known as photosensitizers (PS) due to their inherent ability to absorb  
13                photons of light and transfer that energy to oxygen which then converts to a cytotoxic  
14                or cytostatic species. Table 1 presents a list of classes of photosensitizer compounds  
15                commonly employed in PDT, which PS's are referred to hereinafter in the alternative  
16                as "ROPPs" (Reactive Oxygen Producing Photosensitizer molecules) and "LEPs"  
17                (Light Emitting Photosensitive molecules). While not exhaustive, the list of PDT  
18                photosensitizer drugs presented in Table 1 is exemplary of the variety of ROPPs and  
19                LEPs currently used in the art.

20                The photoactivating device employed for PDT usually comprises a  
21                monochromatic light source such as a laser, the light output of which may be coupled

1 to an invasive light delivery catheter for conduction and delivery to a remote target  
2 tissue. Such interventional light delivery catheters are well known in the art and are  
3 described, for example, in U.S. Patents 5,169,395; 5,196,005; and 5,231,684. Other  
4 devices which are frequently used in conjunction with a light source and light delivery  
5 catheter include drug delivery devices and/or a balloon perfusion catheter (U.S. Patent  
6 5,213,576) and/or various medicament-dispensing stents for the slow localized release  
7 of the photosensitizer. PDT is presently an approved procedure in Canada, Japan, and  
8 The Netherlands for the treatment of various cancers.

9 In addition to cancer therapy, PDT is being tested for the treatment of  
10 psoriasis. Extra-corporal PDT of blood is being evaluated for the prevention of intimal  
11 hyperplasia following transplant surgery. PDT is also being evaluated for the  
12 treatment of vascular disease; most commonly the prevention of intimal hyperplasia  
13 following angioplasty. ROPPs are presently in clinical trials for the treatment of  
14 cutaneous cancers such as basal cell carcinoma, basal cell nevus syndrome, squamous  
15 cell carcinoma, and AIDS related Kaposi's sarcoma. ROPPs are also being  
16 investigated for the treatment of a cancer precursor, Barrett's esophagus. In addition,  
17 ROPPs may have utility for treating invasive cancers, cancer precursors, psoriasis, non-  
18 cancerous urological disorders, viral inactivation, macular degeneration, glaucoma and  
19 various vascular diseases.

1 **Table 1: ROPPs and LEPs**

Pyrrole-derived macrocyclic compounds	Texaphyrins and derivatives thereof (11)
Naturally occurring or synthetic porphyrins and derivatives thereof (1)*	Phenoxazine dyes and derivatives thereof (12)
Naturally occurring or synthetic chlorins and derivatives thereof (2)	Phenothiazines and derivatives thereof (13)
Naturally occurring or synthetic bacterio- chlorins and derivatives thereof (3)	Chalcoorganopyrylium dyes and derivatives thereof (14)
Synthetic isobacteriochlorins and derivatives thereof (4)	Triarylmethanes and derivatives thereof (15)
Phthalocyanines and derivatives thereof (5)	Rhodamines and derivatives thereof (16)
Naphthalocyanines and derivatives thereof (6)	Fluorescenes and derivatives thereof (17)
Porphyccenes and derivatives thereof (7)	Azaporphyrins and derivatives thereof (18)
Porphyccyanines and derivatives thereof (8)	Benzochlorins and derivatives thereof (19)
Pentaphyrin and derivatives thereof (9)	Purpurins and derivatives thereof (20)
Sapphyrins and derivatives thereof (10)	Chlorophylls and derivatives thereof (21)
	Verdins and derivatives thereof (22)

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5 \* (m) refers to the compound having molecular structure indicated at (m) in the

6 specification where m is an integer between 1 and 22.

1           ROPPs and LEPs such as those indicated in Table 1, and as illustrated in  
2        Figures 1-23, have been shown to selectively accumulate, both *in vitro* and *in vivo*, in  
3        catheter induced atheromatous plaques in rabbit and swine models as evidenced by  
4        laser induced fluorescence and chemical extraction (HL Narciso, et al, Retention of tin  
5        ethyl etiopurpurin (SnET2) by atheromatous plaques: Studies in vitro & in vivo  
6        rabbits, *Proceedings of SPIE: Diagnostic and Therapeutic Cardiovascular*  
7        *Interventions IV*, 1994, 2130:30-41). *In vitro* studies utilizing human cadaver aortas  
8        demonstrate the passive accumulation of photosensitizers such as ROPPs and LEPs  
9        into naturally occurring atheromatous plaques. Certain ROPPs and LEPs have the  
10      ability to penetrate the nuclear membrane within a cell and to intercalate into the  
11      nuclear DNA, particularly ROPPs bearing a positive charge (cationic).

12        Psoralen-type compounds have also been investigated for their ability to  
13      prevent intimal hyperplasia. Psoralens and other furocoumarins (furane fused to  
14      coumarin and derivatives thereof) are also photosensitive compounds which have been  
15      used in the treatment of psoriasis for over 40 years. Such psoralen-based phototherapy  
16      is alternatively referred to herein as PUVA; Psoralen activated with UltraViolet A  
17      light. An exemplary list of some furocourmarin compounds is presented in Table 2.  
18       Systemically administered psoralen-type compounds penetrate the nuclear membrane  
19      of cells and may intercalate with the nuclear DNA in target tissue cells. Following  
20      intercalation with the target tissue's nuclear DNA, the psoralen compound is  
21      photoactivated with ultraviolet light or short wavelength visible light (see, for example,  
22      FP Gasparro, et al, The excitation of 8-Methoxysoralen with visible light: Reversed  
23      phase HPLC quantitation of monoadducts and cross-links, *Photochem. Photobiol.*,  
24      1993, 57(6):1007-1010.), which UV light is preferably delivered only to the target

1 tissue by a light delivery catheter or similar delivery device, to cause DNA crosslinking  
2 and ultimately a mutagenic effect in the cells comprising the target tissue. (KL March,  
3 et al, 8-Methoxysoralen and longwave ultraviolet irradiation are a novel  
4 antiproliferative combination for vascular smooth muscle, *Circulation*, 1993, 87:184-  
5 91; BE Sumpio, et al, Control of smooth muscle cell proliferation by psoralen  
6 photochemotherapy, *J. Vasc. Surg.*, 1993, 17:1010-1018; KW Gregory, et al,  
7 Photochemotherapy of intimal hyperplasia using psoralen activated by ultraviolet light  
8 in a porcine model, *Lasers in Surg. Med.*, 1994, (Suppl 6):12 Abstract).

9 Furocoumarins are photochemical agents showing potential for both diagnostic  
10 and therapeutic applications in medicine. The DNA cross-linking by furocoumarins  
11 such as described above proceeds by a two step process. Following injection of the  
12 furocoumarin into the body of an animal, the (planar) furocoumarin molecule first  
13 intercalates within the double helix of intracellular DNA or RNA. Following  
14 intercalation, the covalent addition of the furocoumarin to the polynucleic acid is  
15 achieved through the addition of light energy within the absorption band of the specific  
16 furocoumarin. Either furocoumarin -RNA or -DNA monoadducts or cross-links may  
17 be created upon illumination of the intercalated species. By forming covalent cross-  
18 links with base-pair structures, furocoumarins can alter the metabolic activity of a cell  
19 and induce cytostasis (GD Cimino, HB Gamper, ST Isaacs, JE Hearst, Psoralens as  
20 photoactive probes of nucleic acid structures and function: Organic chemistry, and  
21 biochemistry, *Ann. Rev. Biochem.*, 1985, 54:1154-93).

1   **Table 2: Furocoumarins<sup>†</sup>**

2                   **Compounds containing Furocoumarin sub-components (23)\***

3                   **Psoralens and derivatives thereof (24)**

4                   **Isopsoralens (angelicins) and derivatives thereof (25)**

5                   **Pseudopsoralens and derivatives thereof (26)**

6                   **Pseudoisopsoralens and derivatives thereof (27)**

7                   **Allopsoralens and derivatives thereof (28)**

8                   **Pseudoallopsoralens and derivatives thereof (29)**

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21   \* (m) refers to the compound having the structure indicated at Figure m in the  
22   appended figures where m is an integer  $23 \leq m \leq 29$ .

23   † The furocoumarins may be either naturally occurring or synthetic.

1           Coronary artery disease is thought to be initiated by a disruption of fatty  
2 streaks which form early in life on the vessel wall which disruption, in turn, promotes  
3 thrombus formation. Over time the thrombus becomes organized and provides  
4 structure for the accumulation of fatty lipids, foam cells, cholesterol, calcium, fibrin,  
5 and collagen. A fibrous cap forms over this collection of lipid-rich material.  
6 Periodically this fibrous cap ruptures; releasing some of the lipid-rich material and  
7 exposing the remaining plaque materials to the circulating blood. Growth factors  
8 within the blood initiate the migration of smooth muscle cells (SMCs), from the media  
9 to the intima where proliferation of the SMCs begins. The ulcerated plaque induces  
10 the deposition of platelets and thrombus formation in a "response to injury" mode.  
11 This cycle recurs until eventually the plaque ruptures, the distal coronary artery is  
12 occluded by an thrombus and a heart attack occurs (V. Fuster, et al, Clinical-  
13 Pathological Correlations of Coronary Disease Progression and Regression,  
14 Supplement to Circulation, Vol. 86, No. 6, 1992:III-1-III-11 and JJ Badimon,  
15 Coronary Atherosclerosis, A Multifactorial Disease, Supplement to Circulation, Vol.  
16 87, No. 3, 1993:II-3-II-16).

17           Restenosis occurs when coronary disease is treated with an interventional  
18 therapy such as Percutaneous Transluminal Coronary Angioplasty, PTCA, or  
19 atherectomy, or laser angioplasty, or stenting, or a myriad of newer technologies.  
20 Restenosis refers to the over- aggressive autogenous repair of an injury to a blood  
21 vessel by the body. Intimal hyperplasia or the hyperproliferation of medial (and  
22 possibly adventitial) smooth muscle cells (SMCs,) is a major contributing factor to  
23 restenosis. Hyperproliferating SMCs form a neo-intima which can reduce the bore of  
24 the arterial lumen and thus the capacity of the artery to deliver oxygen rich blood. This

1 reduction in cross-sectional luminal area can be more severe than the original  
2 constricted area which was treated. The foregoing problems are representative of  
3 some medical conditions which the compounds of the present invention may have  
4 particular application.

5 DNA cross-linking by furocoumarins results in the reduction of smooth muscle  
6 cell (SMC) proliferation and, since their DNA cross-linking activity is cytostatic,  
7 furocoumarins may have certain advantages over cytotoxic photosensitizers (ROPPs  
8 and LEPs) in the prevention of intimal hyperplasia as described by March, et al, U.S.  
9 Patent 5,116,864 and Deckelbaum, et al, U.S. Patent 5,354,774 the teachings of  
10 which patents are incorporated herein by reference thereto. The cytotoxicity of  
11 ROPPs and LEPs currently used in PDT results in the extravasation of intracellular  
12 organelles, cytoplasm, and cytokines which, in turn, elicits an inflammatory response.  
13 The inflammatory response elicited by extravasation of cellular contents is  
14 hypothesized as a key contributing factor to restenosis. The disadvantage of  
15 employing psoralens to prevent restenosis (when compared to photosensitizers such as  
16 ROPPs and LEPs) is that psoralens do not exhibit a selective affinity for atheromatous  
17 plaques over normal intimal tissue.

18

## 19 SUMMARY OF THE INVENTION

20 It is a primary object of the present invention to provide a photoactivatable  
21 compound which can be used to treat a variety of diseases.

22 It is an object of the present invention to provide a photoactivatable therapeutic  
23 compound which causes cytostasis but not cytolysis when bound to a cell and activated  
24 with light.

1        It is another object of the present invention to provide a photoactivatable  
2 compound which has a selective affinity for rapidly proliferating cells.

3        It is still a further object of the present invention to provide a photoactivatable  
4 compound which will reduce the incidence of restenosis following phototherapy of  
5 atheromatous plaque.

6        It is a further object of the present invention to provide a photoactivatable  
7 compound which can cause cytostasis when activated by a specific wavelength of light.

8        It is still a further object of the present invention to provide a photoactivatable  
9 compound which can cause cytostasis when activated by one particular wavelength of  
10 light and cause cytolysis when activated with light having a different wavelength.

11       It is yet a further object of the present invention to provide a method for  
12 treating such diseases as atherosclerosis, restenosis, cancer, cancer precursors,  
13 noncancerous hyperproliferative diseases, psoriasis, macular degeneration, glaucoma  
14 and viruses employing photoactivatable compounds.

15       It is a further object of the present invention to provide a method for employing  
16 such photoactivatable compounds for diagnosing such diseases as atherosclerosis,  
17 restenosis, cancer, cancer precursors, noncancerous hyperproliferative diseases,  
18 psoriasis, macular degeneration, glaucoma and viruses.

19       The features of the invention believed to be novel are set forth with  
20 particularity in the appended claims. However, the invention itself, both as to  
21 composition and manner of use, together with further advantages of these compounds  
22 may best be understood by reference to the following description of preferred  
23 embodiments.

1

BRIEF DESCRIPTION OF THE FIGURES

2 Figures 1-22 present the chemical structures of various photosensitive pyrrole-  
3 derived macrocyclic compounds which exhibit as follows:

4 Figure 1 illustrates the chemical structure of photoactivatable compositions  
5 comprising a porphyrin core.

6 Figure 2 shows clorin compounds.

7 Figure 3 shows bacteriochlorin-derived compounds.

8 Figure 4 illustrates isobacteriochlorin compounds

9 Figure 5 shows phthalocyanines.

10 Figure 6 shows naphthalocyanine compounds.

11 Figure 7 illustrates porphycene-containing compounds.

12 Figure 8 is porphycyanine compounds.

13 Figure 9 is pentaphyrin derivatives.

14 Figure 10 shows sapphyrin and derivatives thereof.

15 Figure 11 illustrates texaphyrin and derivatives thereof.

16 Figure 12 shows the chemical structures of phenoxazine dyes and derivatives  
17 thereof.

18 Figure 13 is phenothiazine and derivatives thereof.

19 Figure 14 illustrates chalcoorganopyrylium dyes.

20 Figure 15 shows triarylmethane derivatives.

21 Figure 16 gives the structure of rhodamine and derivatives thereof.

22 Figure 17 is fluorescene derivatives.

23 Figure 18 shows azaporphyrin and derivatives thereof.

24 Figure 19 shows benzochlorin and derivatives thereof.

- 1       Figure 20 illustrates the structure of purpurin and derivatives thereof.
- 2       Figure 21 shows chlorophyll and derivatives thereof.
- 3       Figure 22 is verdin and derivatives thereof.
- 4       Figure 23 shows the chemical structure of compounds containing furocoumarin  
5       sub-components.
- 6       Figure 24 illustrates psoralens and derivatives thereof.
- 7       Figure 25 shows the structure of isopsoralens (angelicins) and derivatives  
8       thereof.
- 9       Figure 26 is the chemical structure of pseudopsoralens and derivatives thereof.
- 10      Figure 27 illustrates the chemical structure of pseudoisopsoralen compounds.
- 11      Figure 28 shows allopsoralen and derivatives thereof.
- 12      Figure 29 is pseudoallopsoralen and derivatives thereof.
- 13

#### 14           **DESCRIPTION OF THE PREFERRED EMBODIMENTS**

15      A problem encountered when using conventional cytotoxic photosensitizer  
16     compounds such as those listed in Table 1 for PDT is the post-administration  
17     inflammatory sequella such as restenosis of a blood vessel. While photosensitizers  
18     such as ROPPs and LEPs exhibit enhanced selectivity and avidity for rapidly  
19     proliferating cells in comparison with normal, more quiescent cells, the cytotoxic and  
20     cytolytic activity of such compounds may be undesirable.

21      A problem encountered when using PUVA for the treatment of  
22     hyperproliferative conditions is that furocoumarins exhibit little, if any, specificity and  
23     avidity for hyperproliferative cells over normal cells. Notwithstanding the foregoing,  
24     furocoumarins have the advantage that upon photoactivation with light they may

1 either form a monoadduct to DNA or crosslink the nuclear DNA, thereby rendering  
2 the cell quiescent. Such cytostatic activity does not produce inflammation to the same  
3 extent as PDT employing ROPPs and LEPs. A novel class of photosensitizer  
4 compounds exhibiting the enhanced specificity of ROPPs and LEPs for  
5 hyperproliferating cells and the photocytostatic activity of furocoumarin compounds is  
6 described.

7 The compounds of the present invention form a super-class of compounds  
8 characterized by a furocoumarin compound or component thereof, alternatively  
9 referred to hereinafter as "F", conjugated with one or more of the following  
10 photosensitive molecules: (a) a ROPP (Reactive Oxygen Producing Photosensitizer) or  
11 a component thereof; or (b) a LEP (Light Emitting Photosensitizer) or a component  
12 thereof to form a F-ROPP or F-LEP. The individual compounds within this super-  
13 class of compounds are useful for the diagnosis and treatment of a myriad of diseases  
14 as previously described. F-ROPPs contained within this super-class of compounds are  
15 classes of compounds containing all possible combinations of any of the compounds  
16 set forth in Table 1 conjugated to compounds listed in Table 2. Additional compounds  
17 not explicitly listed in Tables 1 and 2 which exhibit the photosensitive and/or tissue  
18 specificity properties exemplified by ROPPs or LEPs conjugated to furocoumarins (F-  
19 ROPPs) should be construed as included within, and part of, this super-class of  
20 compounds. Each class of compound contains a plethora of specific compounds  
21 differing only in the particular functional groups attached to the basic structure.

22 For example, furocoumarins and derivatives thereof can be conjugated with  
23 porphyrins, chlorins, bacteriochlorins, isobacteriochlorins, phthalocyanines,  
24 naphthalocyanines, porphycenes, porphycyanines, pentaphyrin, sapphyrins,

1 texaphyrins, phenoxazine dyes, phenothiazines, chaloorganopyrylium dyes,  
2 rhodamines, fluorescenes, azoporphyrins, benzochlorins, purpurins, chlorophylls,  
3 verdins and triarylmethanes and derivatives thereof, thereby creating 23 new classes of  
4 compounds. Compounds within each class are conveniently referred by first specifying  
5 the particular furocoumarin followed by the particular ROPP or LEPP. For example,  
6 isopsoralen conjugated with chlorin would be isopsorachlorin.

7 As a further example, furocoumarins such as naturally occurring or synthetic  
8 psoralens, as well as derivatives thereof, can be conjugated with one of the following  
9 photosensitive compounds from Table 1: porphyrins, chlorins, bacteriochlorins,  
10 synthetic isobacteriochlorins, phthalocyanines, naphthalocyanines, porphycenes,  
11 porphycyanines, pentaphyrin, sapphyrins, texaphyrins, phenoxazine dyes,  
12 phenothiazines, chaloorganopyrylium dyes, rhodamines, fluorescenes, azoporphyrins,  
13 benzochlorins, purpurins, chlorophylls, verdins and triarylmethanes, as well as  
14 derivatives of such photosensitizers. The foregoing conjugates form new classes of  
15 compounds which may conveniently be referred to, for example, as: Psoraporphyrins,  
16 Psorachlorins, Psora-bacteriochlorins, Psoraisobacteriochlorins, Psoraphthalocyanines,  
17 Psoranaphthalocyanines, Psoraporphycenes, Psoraporphycyanines, Psorapentaphyrin,  
18 Psorasapphyrins, Psoratexaphyrins, Psoraphenoxazine dyes, Psoraphenothiazines,  
19 Psorachaloorgana-pyrylium dyes, Psorarhodamines, Psorafluorescenes,  
20 Psoraazaporphyrins, Psorabzeno-chlorins, Psorapurpurins, Psorachlorophylls,  
21 Psoraverdins, and Psoratriarylmethanes, and derivatives thereof, respectively.

22 The following examples presenting the synthesis of particular photosensitizer  
23 compounds in accordance with the present invention are representative of the variety

1 of photoactive furocoumain-photosensitizer conjugates which can be made and the  
2 conditions therefor.

3  
4 Example 1.

5 Pyropheophorbide linked 8-MOP. (8-MOP PPh<sub>e</sub>)

6 Pyropheophorbide (300mg) was dissolved in dry tetrahydrofuran (100mL) and  
7 1,3-dicyclohexylcarbodiimide (100mg) and dimethylaminopyridine (100mg) were  
8 added. After stirring at room temperature for 15 min., a solution of 5-aminomethyl-8-  
9 methoxysoralen (250mg) in dry tetrahydrofuran (60mL) was added. The solution was  
10 stirred at room temperature overnight. The solvent was removed by rotary  
11 evaporation, and the residual solid dissolved in dichloromethane, washed with dilute  
12 HCl then sodium carbonate solution. The organic layer was collected, dried over  
13 sodium sulfate, filtered and evaporated to dryness on a rotary evaporator. The crude  
14 residue was chromatographed on silica using methanol / dichloromethane (2%) and the  
15 major green band collected and evaporated. The residue, 8  
16 Methoxysorapyropheophorbide (Structure I below), was crystallized from  
17 dichloromethane / methanol.

18

19 Example 2.

20 Meso-Pyropheophorbide linked 8-MOP. (8-MOP MPPhe)

21 Meso-Pyropheophorbide (300mg) was dissolved in dry tetrahydrofuran  
22 (100mL) and 1,3-dicyclohexylcarbodiimide (100mg) and dimethylaminopyridine  
23 (100mg) were added. After stirring at room temperature for 15 min., a solution of 5-  
24 aminomethyl-8-methoxysoralen (250mg) in dry tetrahydrofuran (60mL) was added.

1 The solution was stirred at room temperature overnight. The solvent was removed by  
2 rotary evaporation, and the residual solid dissolved in dichloromethane, washed with  
3 dilute HCl then sodium carbonate solution. The organic layer was collected, dried over  
4 sodium sulfate, filtered and evaporated to dryness on a rotary evaporator. The crude  
5 residue was chromatographed on silica using methanol / dichloromethane (2%) and the  
6 major green band collected and evaporated. The residue, 8-  
7 Methoxymesopyropeophorbide (Structure II below), was crystallized from  
8 dichloromethane / methanol.

9

10 Example 3.

11 2-(1-Hexyloxyethyl) pyropheophorbide linked 8-MOP. (8-MOP HPPhe)  
12 2-(1-Hexyloxyethyl) pyropheophorbide (200mg) was dissolved in dry  
13 tetrahydrofuran (100mL) and 1,3-dicyclohexylcarbodiimide (100mg) and  
14 dimethylaminopyridine (100mg) were added. After stirring at room temperature for 15  
15 min., a solution of 5-aminomethyl-8-methoxysoralen (170mg) in dry tetrahydrofuran  
16 (60mL) was added. The solution was stirred at room temperature overnight. The  
17 solvent was removed by rotary evaporation, and the residual solid dissolved in  
18 dichloromethane, washed with dilute HCl then sodium carbonate solution. The organic  
19 layer was collected, dried over sodium sulfate, filtered and evaporated to dryness on a  
20 rotary evaporator. The crude residue was chromatographed on silica using methanol /  
21 dichloromethane (2%) and the major green band collected and evaporated. The  
22 residue, 8-MOP HPPhe (Structure III), was crystallized from dichloromethane /  
23 methanol.

1    Example 4.2        Octaethylbenzochlorin linked 8-MOP. (8-MOP OEBCS)

3        To a stirred solution of octaethylbenzochlorin sulfonylchloride (300mg) in dry  
4        dichloromethane (50mL), was added 5-aminomethyl-8-methoxypsoralen (170mg) in  
5        dry dichloromethane (20ml) and dry triethylamine (0.1mL). The resulting solution was  
6        stirred at room temperature for 1 hr and the solvent removed by rotary evaporation.  
7        The crude residue was columned on silica using dichloromethane and the major grey  
8        band collected and recrystallized from dichloromethane / methanol to give the title  
9        compound (Structure IV below).

10

11      Example 5.12        Zinc octaethylbenzochlorin linked 8-MOP. (8-MOP ZnOEBCS)

13        To a stirred solution of octaethylbenzochlorin sulfonylchloride (300mg) in  
14        dichloromethane (50mL), was added 5-aminomethyl-8-methoxypsoralen (150mg) in  
15        dichloromethane (20ml) and dry triethylamine (0.1mL). The resulting solution was  
16        stirred at room temperature for 1 hr. Zinc acetate (200mg) dissolved in methanol  
17        (10mL) was added to the reaction solution and the solution was warmed on a hot  
18        water bath until metallation of the benzochlorin was complete by Uv / vis spectroscopy  
19        (as seen by a band I absorption at 673nm). The solvent was then removed by rotary  
20        evaporation and the crude residue redissolved in dichloromethane (5mL) and  
21        chromatographed on silica using dichloromethane. The major green band collected and  
22        recrystallized from dichloromethane / methanol to give the title compound (Structure  
23        V below).

24

1    Example 6.

2                Cu iminium octaethylbenzochlorin linked 8-MOP. (8-MOP Cu Im OEBCS)

3                To copper octaethylbenzochlorin sulfonic acid (300mg) dissolved in  
4                dichloromethane (100mL) was added (chloromethylene) dimethylammonium chloride  
5                (500mg) and the solution stirred overnight at room temperature, protected from  
6                moisture. The solution was poured into ice cold water quickly, the organic layer  
7                washed with water rapidly, separated and dried over sodium sulfate. The solution was  
8                filtered to remove sodium sulfate and 5-aminomethyl-8-methoxysoralen (200mg) in  
9                dichloromethane (20mL) was added. The solution was stirred for 20 minutes at room  
10              temperature, then poured into water. The organic layer was washed with dilute HCl  
11              and dried over sodium sulfate. The solution was filtered and evaporated to dryness.  
12              The resulting residue was chromatographed on silica using 2% methanol /  
13              dichloromethane and the major green band collected and evaporated. The title  
14              compound (Structure VI below) was obtained as a green powder by precipitation from  
15              dichloromethane / hexane.

16

17    Example 7.

18                Indium texaphyrin linked 8-MOP. (8-MOP InT)

19                To a solution of Indium texaphyrin-16-carboxylic acid (200mg) was dissolved  
20              in dry terahydrofuran (50mL) and 1,3-dicyclohexylcarbodiimide (50mg) and  
21              dimethylaminopyridine (50mg) added. After stirring at room temperature for 15 min., a  
22              solution of 5-aminomethyl-8-methoxysoralen (100mg) in dry terahydrofuran (20mL)  
23              was added. The solution was stirred under argon at room temperature overnight. The  
24              solvent was removed by rotary evaporation, and the residual solid dissolved in

1 dichloromethane and washed with dilute HCl and finally with water. The organic phase  
2 was separated, dried over sodium sulfate, revaporated under reduced pressure and  
3 chromatographed on silica using methanol / dichloromethane (2%). The major green  
4 band was collected and evaporated. The residue, 8-MOP InT (Structure VIII below),  
5 was crystallized from dichloromethane / hexane.

6

7 Example 8.

8 Protoporphyrin linked 8-MOP. (8-MOP PP)

9 Protoporphyrin (200mg) was dissolved in oxalyl chloride (3mL) and the  
10 solution warmed at 40°C for 1hr, while being protected from moisture. The excess  
11 oxalyl chloride was removed under high vacuum and dry dichloromethane (5mL) was  
12 added. This was also removed under high vacuum, to give a purple residue that was  
13 protected from moisture via a drying tube. Dry dichloromethane (10mL) and dry  
14 triethylamine (1mL) were added to the residue, followed by a solution of 5-  
15 aminomethyl-8-methoxysoralen (160mg) in dry dichloromethane (20mL). The  
16 solution was stirred overnight, protected from moisture via a drying tube. The solution  
17 was then poured into water and the organic phase washed well with water, collected  
18 and dried over sodium sulfate. After filtration and evaporation to dryness, the resulting  
19 residue was columned on silica using 2% acetone / dichloromethane as eluent. The  
20 major red band was collected and recrystallized from dichloromethane / methanol to  
21 yield the title compound VIII.

22

1    Example 9.2        Tetraphenylporphyrin linked 8-MOP. (8-MOP TPP)

3           Meso-terakis-(4'-carboxyphenyl) porphyrin (200mg) was dissolved in oxalyl  
4           chloride (5mL) and the solution warmed at 40°C for 1hr, while being protected from  
5           moisture. The excess oxalyl chloride was removed under high vacuum and dry  
6           dichloromethane (5mL) was added. This was also removed under high vacuum, to  
7           give a green residue that was protected from moisture via a drying tube. Dry  
8           dichloromethane (10mL) and dry triethylamine (1mL) were added to the residue and a  
9           solution of 5-aminomethyl-8-methoxysoralen (400mg) in dry dichloromethane  
10          (20mL) was added. The solution was stirred overnight, protected from moisture via a  
11          drying tube. The solution was then poured into water and the organic phase washed  
12          well with water, collected and dried over sodium sulfate. After filtration and  
13          evaporation to dryness, the resulting residue was columned on silica using 2% acetone  
14          / dichloromethane as eluent. The major red band comprised 8-MOP TPP (Structure  
15          IX) and was collected and recrystallized from dichloromethane / methanol.

16

17      Example 10.18        2,8,12,18-Tetraethyl-3,7,13,17-tetramethyl-5,15-bis(2'-furan) porphyrin. (5,15-  
19        DFP).

20           4,4'-Diethyl-3,3'-dimethyl-2,2'-dipyrromethane (4.0g) and 2-furaldehyde  
21          (1.67g) were dissolved in methanol (100mL) and the solution deaerated by bubbling  
22          with argon for 15min. 4-Toluenesulfonic acid (0.95g) was added and the solution  
23          stirred for 2hrs in the dark, then refrigerated overnight. The precipitated porphyrinogen  
24          was collected, washed with ice cold methanol (20mL) and resuspended in methanol

1 (100mL). o-Chloranil (6.0g) was added and the solution stirred in the dark for 2hrs.  
2 Triethylamine (2mL) was added and the precipitated porphyrin was collected by  
3 filtration, washed well with methanol and dried under high vacuum. The porphyrin was  
4 recrystallized from dichloromethane / methanol to yield the title compound (X).

5

6 Example 11.

7 Texas red linked 8-MOP. (8-MOP TR)

8 Sulforhodamine 101 acid chloride (200mg) was dissolved in dry  
9 tetrahydrofuran (100mL) and 5-aminomethyl-8-methoxysoralen (100mg) added,  
10 followed by triethylamine (0.1mL). The solution was left overnight at room  
11 temperature. The following day the solution was evaporated to dryness, redissolved in  
12 dichloromethane and columned on silica using 2% methanol / dichloromethane as  
13 eluent. The major fluorescent red fraction was collected and evaporated to dryness.  
14 The residue, comprising 8-MOP TR (Structure XI) was recrystallized from  
15 dichloromethane / hexane.

16

17 Example 12.

18 Rhodamine B linked 8-MOP. (8-MOP RB)

19 Sulforhodamine B acid chloride (200mg) was dissolved in dry tetrahydrofuran  
20 (100mL) and 5-aminomethyl-8-methoxysoralen (100mg) added, followed by dry  
21 triethylamine (0.1mL). The solution was left overnight at room temperature. The  
22 following day the solution was evaporated to dryness, redissolved in dichloromethane  
23 and columned on silica using 2% methanol / dichloromethane as eluent. The major

1 fluorescent red fraction was collected and evaporated to dryness. The residue  
2 (Structure XII) was recrystallized from dichloromethane / hexane.

3

4 Example 13.

5 Porphocyanine linked 8-MOP. (8-MOP Pocy)

6 2,3,21,22-tetraethyl-12-(4'-carboxyphenyl) porphocyanine (200mg) was  
7 dissolved in dry tetrahydrofuran (100mL) and 1,3-dicyclohexylcarbodiimide (100mg)  
8 and dimethylaminopyridine (100mg) were added. After stirring at room temperature  
9 for 15 min., a solution of 5-aminomethyl-8-methoxysoralen (300mg) in dry  
10 tetrahydrofuran (60mL) was added. The solution was stirred at room temperature  
11 overnight. The solvent was removed by rotary evaporation, and the residual solid  
12 dissolved in dichloromethane, washed with dilute HCl then sodium carbonate solution.  
13 The organic layer was collected, dried over sodium sulfate, filtered and evaporated to  
14 dryness on a rotary evaporator. The crude residue was chromatographed on silica  
15 using methanol / dichloromethane (2%) and the major green band collected and  
16 evaporated. The residue (Structure XIII) was crystallized from dichloromethane /  
17 methanol.

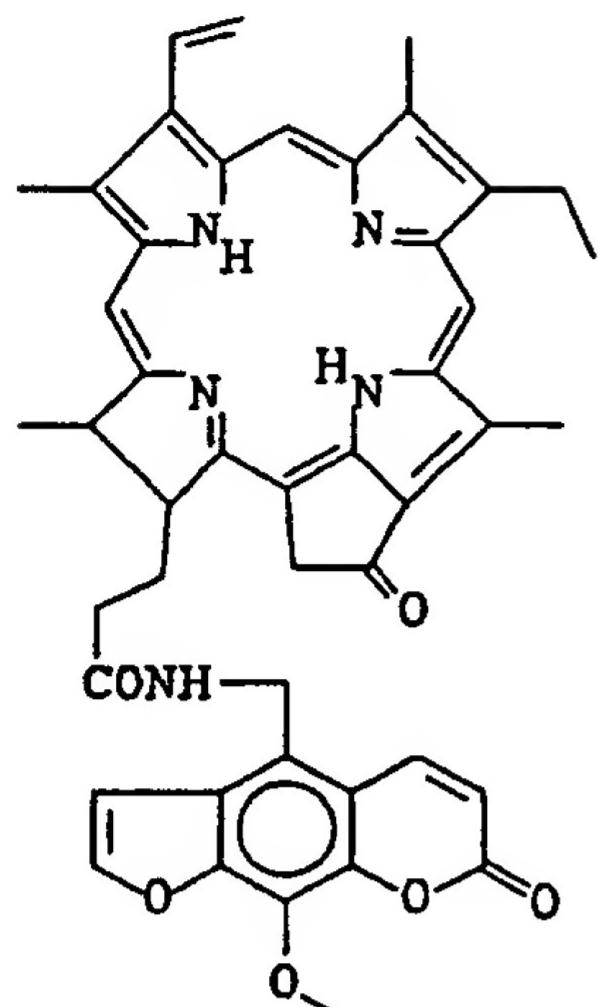
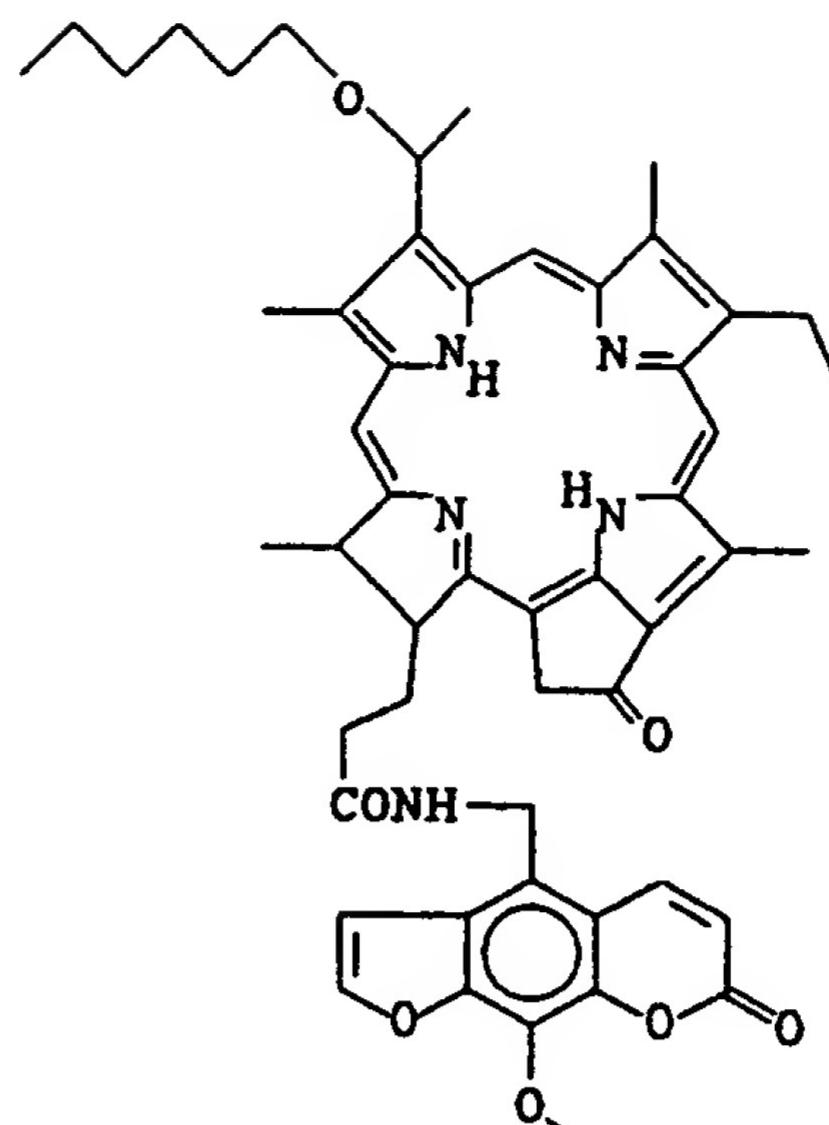
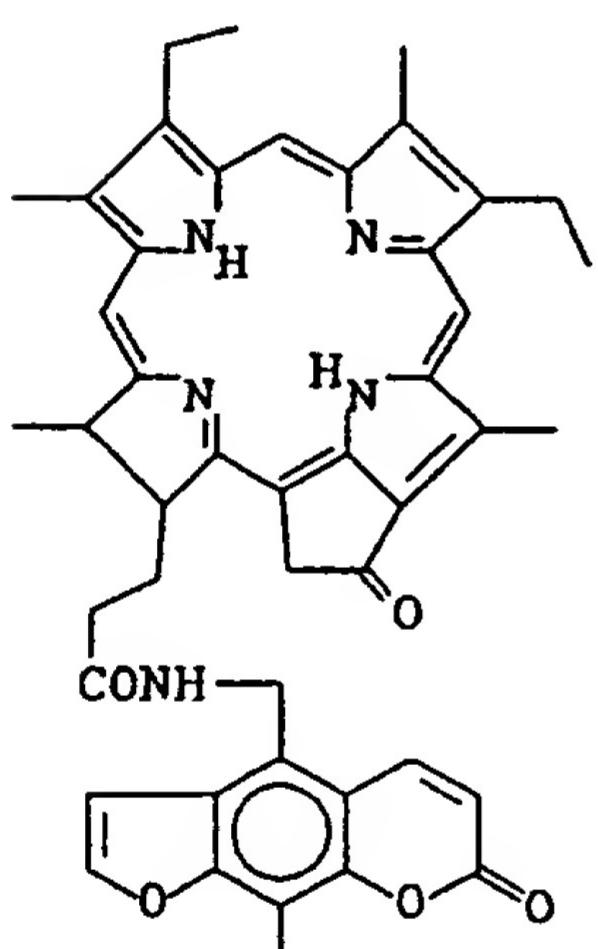
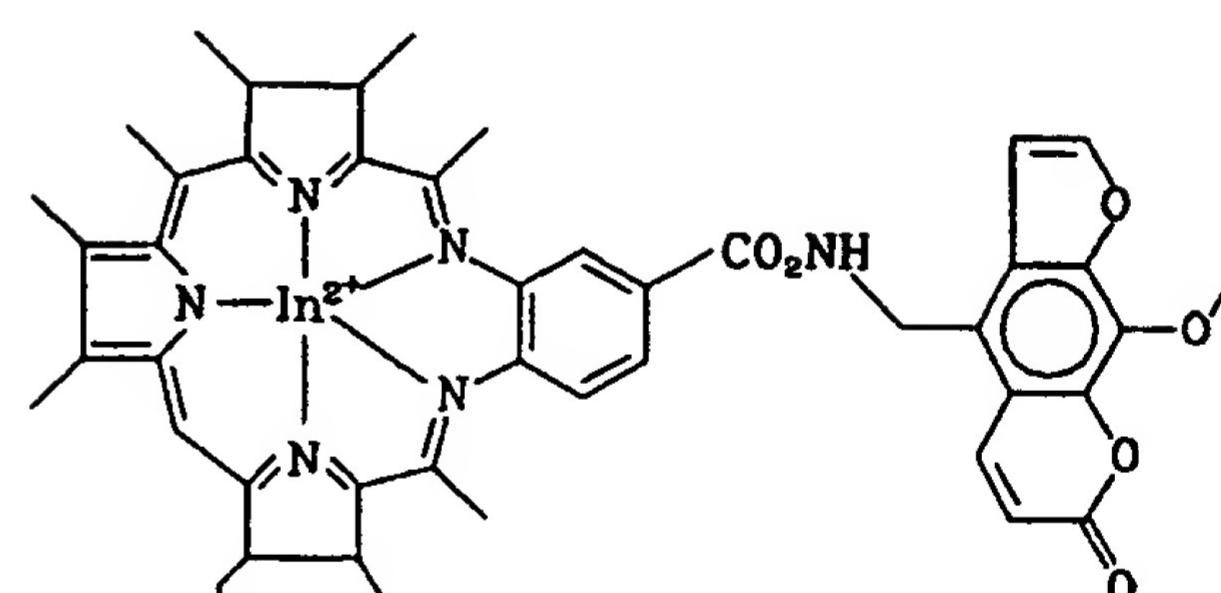
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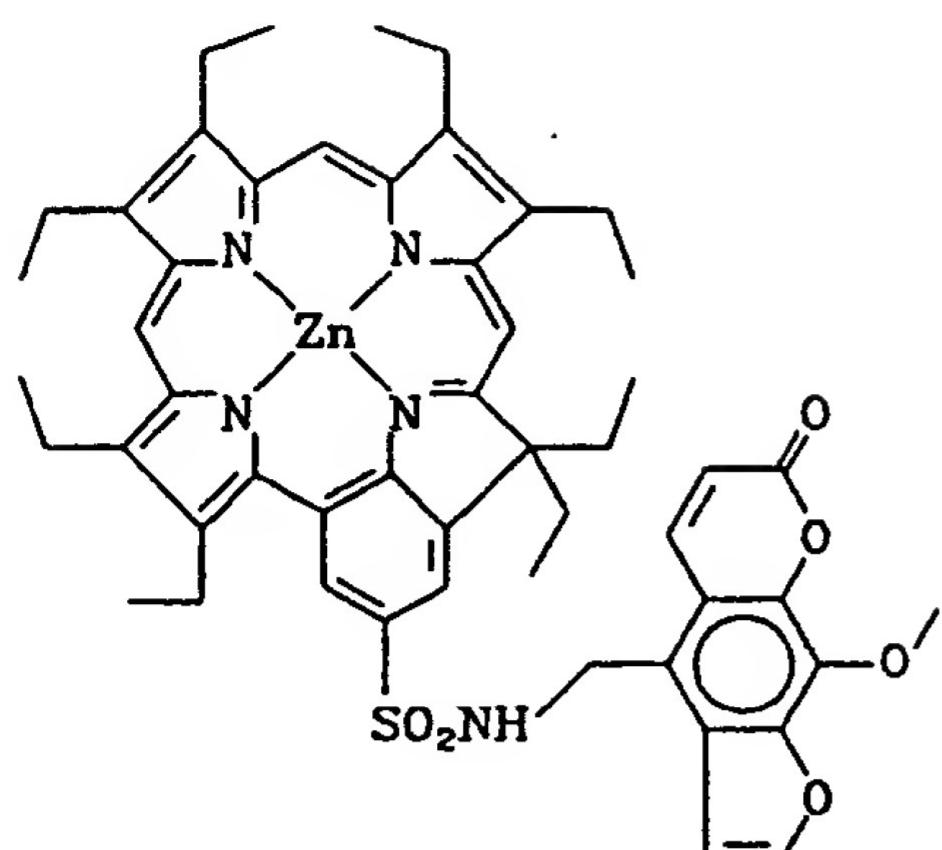
19 Example 14.

20 Phthalocyanine linked 8-MOP. (8-MOP Pth)

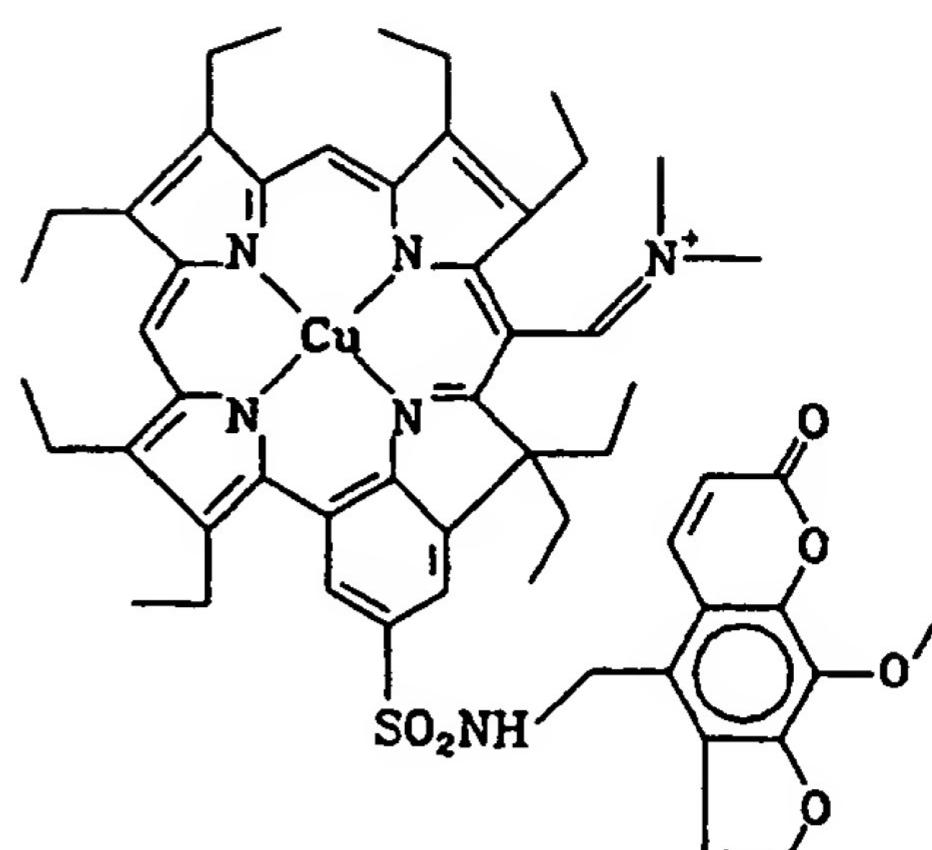
21 Phthalocyanine tetra sulfonate (200mg) was dissolved in phosphorus  
22 oxychloride (20mL) and the solution refluxed for 2 hrs. The excess phosphorus  
23 oxychloride was removed by rotary evaporation and the residue dissolved in dry, cold  
24 pyridine (10mL). A solution of 5-aminomethyl-8-methoxysoralen (300mg) in dry

1 pyridine (60mL) was added. The solution was stirred at room temperature overnight.  
2 The solvent was removed by rotary evaporation, and the residual solid dissolved in  
3 dichloromethane, washed with dilute HCl then sodium carbonate solution. The organic  
4 layer was collected, dried over sodium sulfate, filtered and evaporated to dryness on a  
5 rotary evaporator. The crude residue was chromatographed on silica using methanol /  
6 dichloromethane (5%) and the major green band collected and evaporated. The residue  
7 (Structure XIV) was crystallized from dichloromethane / methanol.

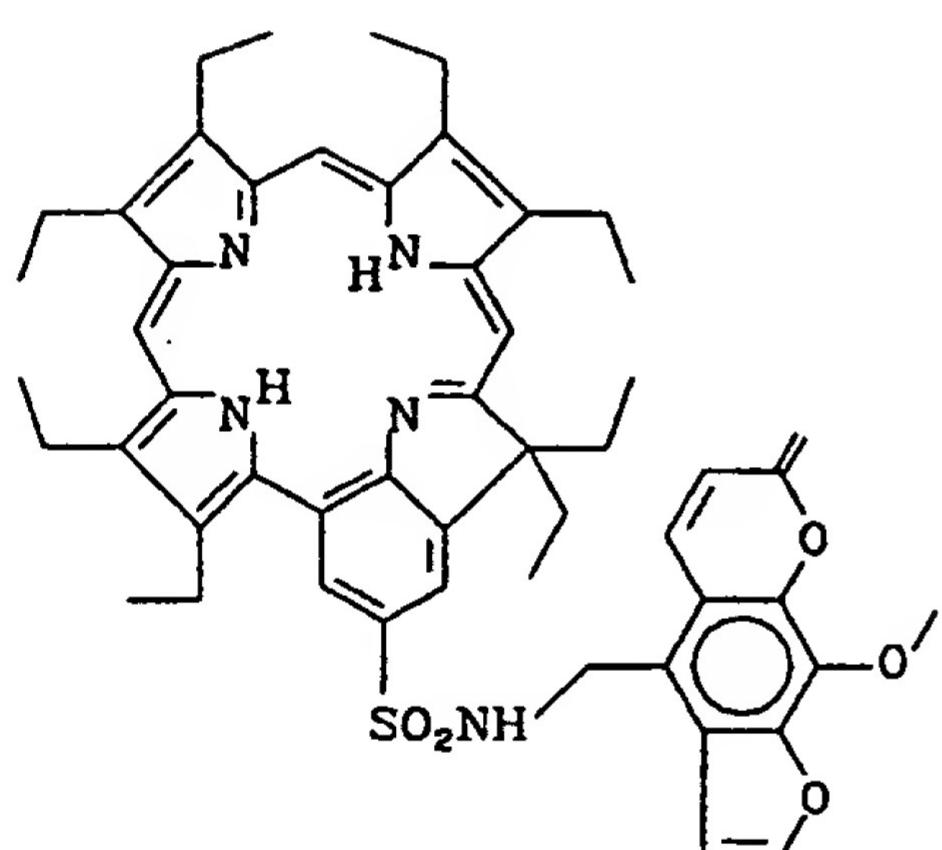
(8-MOP PPhenyl)  
I8-MOP HPPhe  
III8-MOP PPhenyl  
II1  
28-MOP InT  
VII



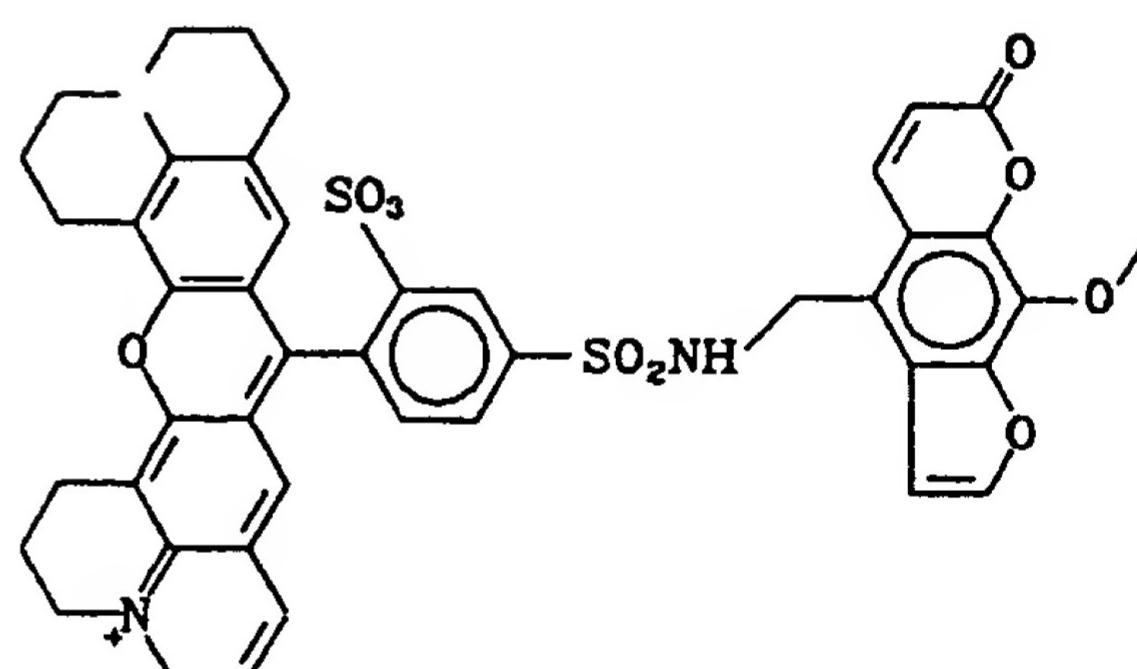
**8-MOP ZnOEBCS  
V**



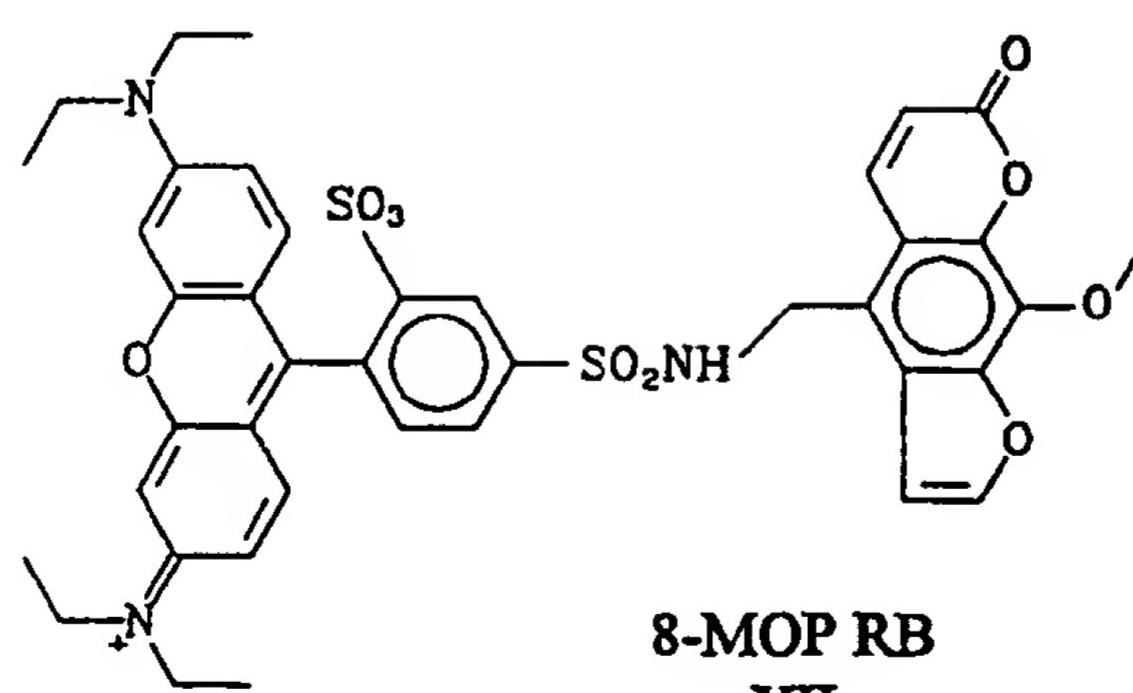
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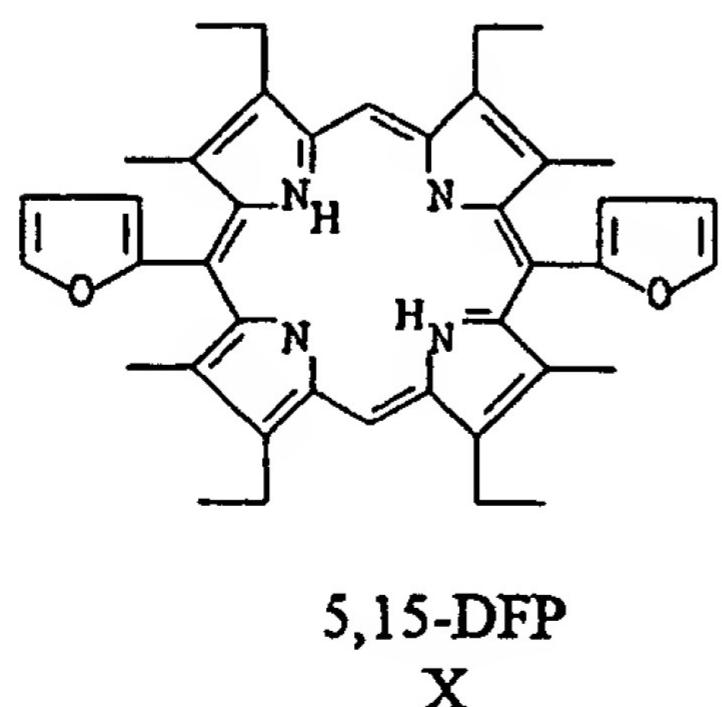
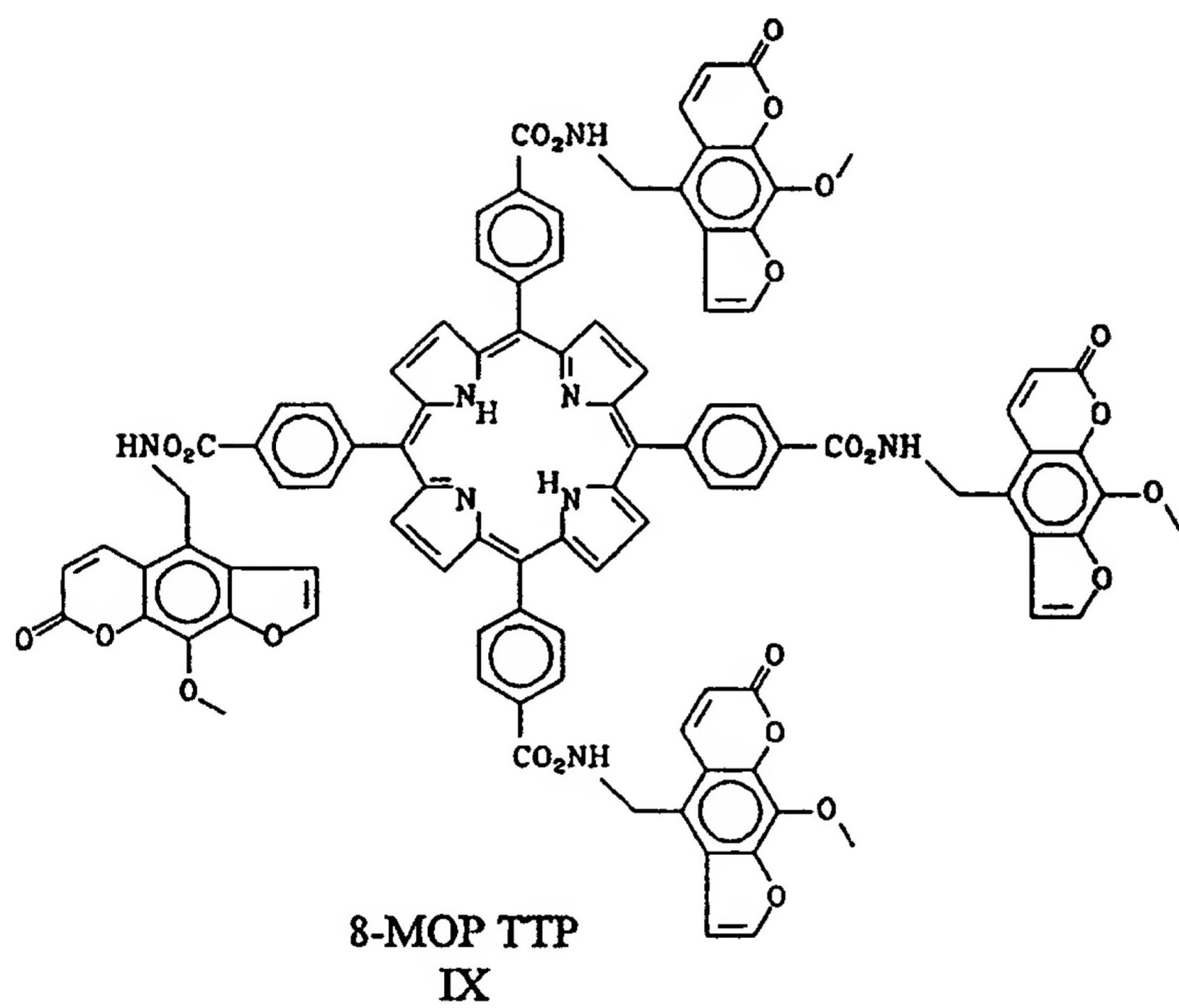
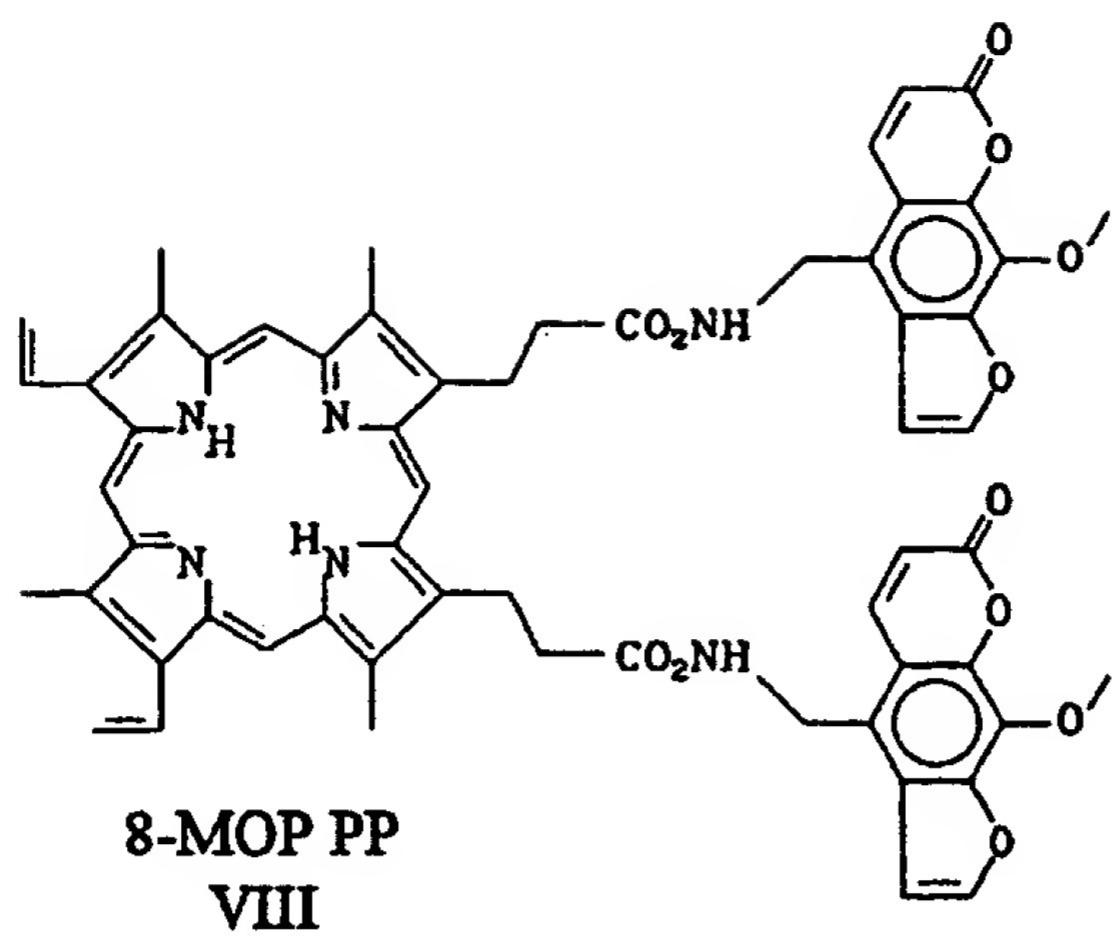
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IV**

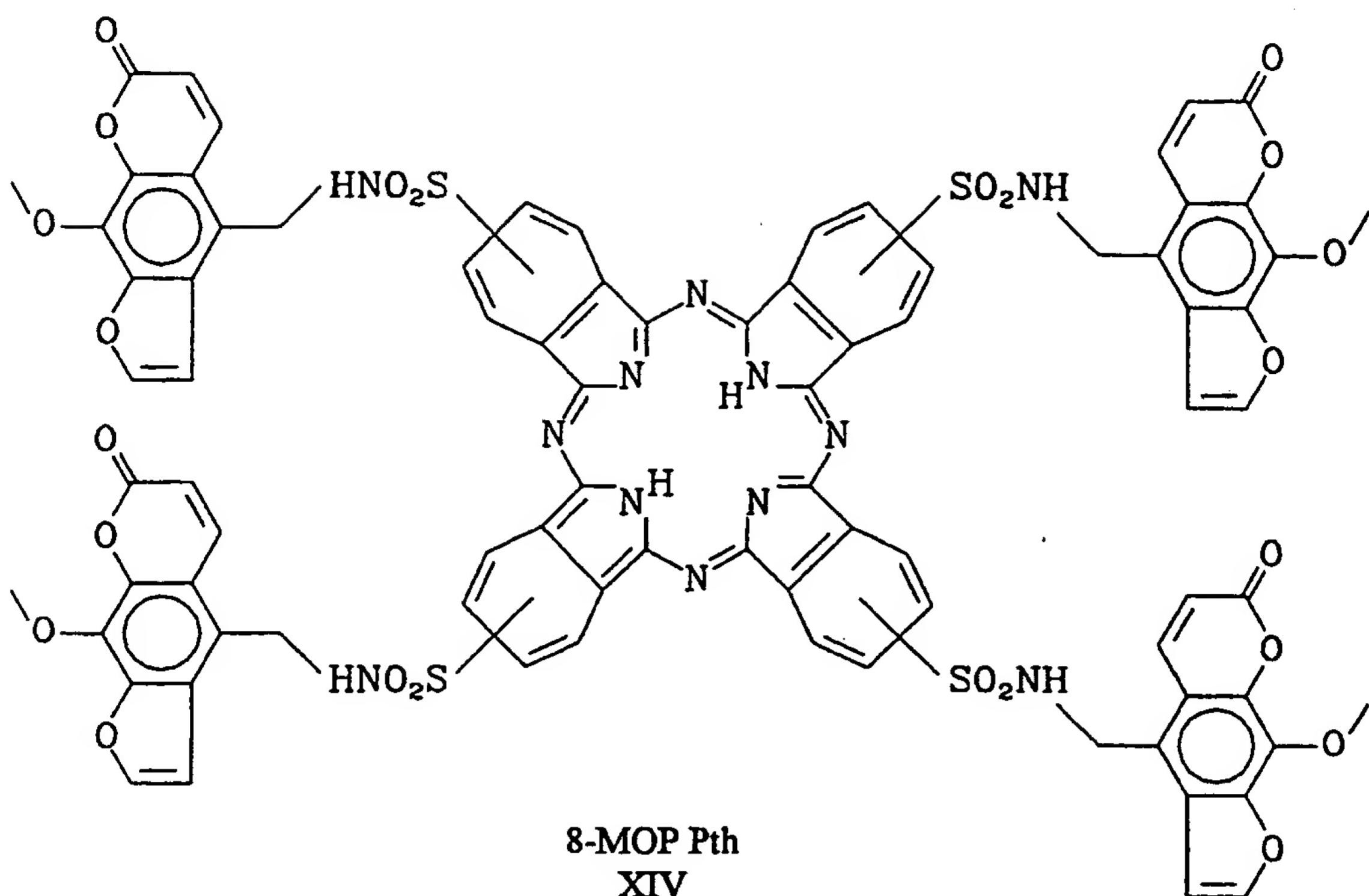


**8-MOP TR  
XI**

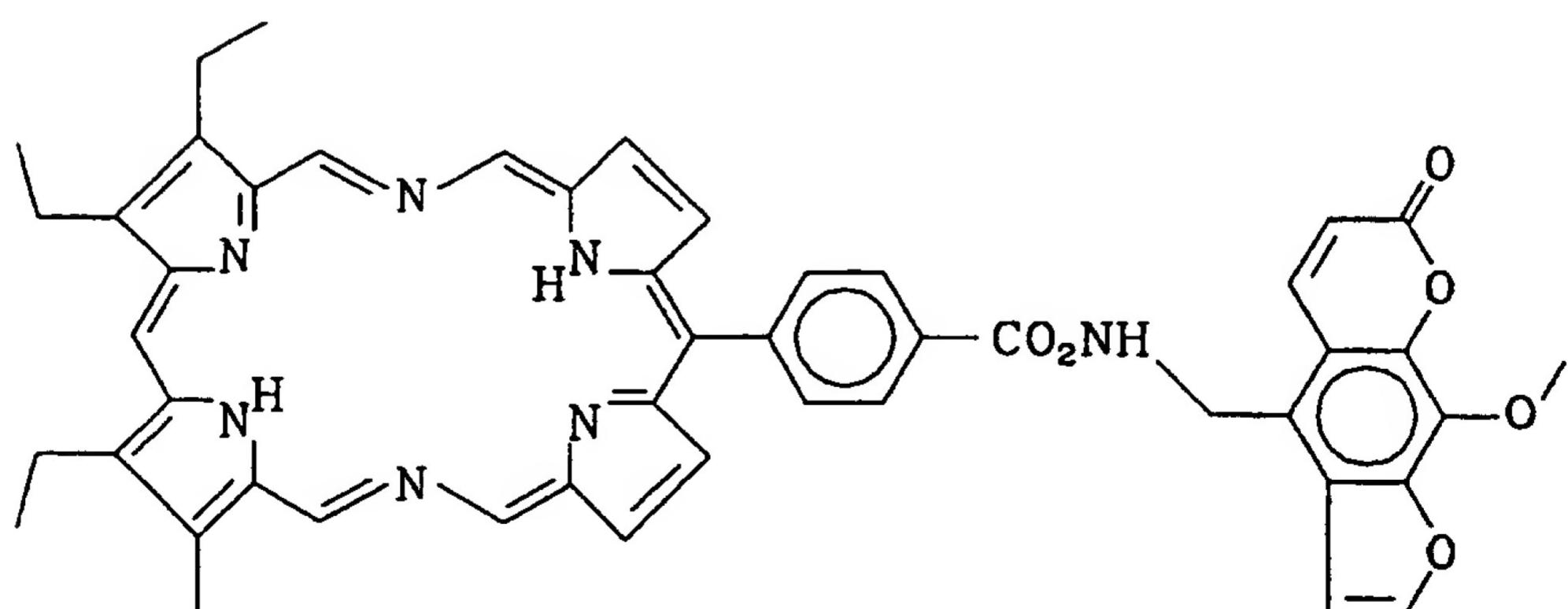


**8-MOP RB  
XII**





8-MOP Pth  
XIV



8-MOP Pocy  
XIII

1       The preceding super-class of photosensitizing compounds may be characterized  
2    by: a) a furocoumarin attached to a Reactive Oxygen Producing Photosensitizer type  
3    compound, F-ROPP; b) a furocoumarin sub-component attached to a ROPP, FS-  
4    ROPP; c) a cationic furocoumarin attached to an ROPP (neutral or cationic), to  
5    produce either CF-ROPP or CFS-ROPP; d) a cationic ROPP attached to a  
6    furocoumarin (neutral or cationic); e) any one of the above compounds wherein the  
7    ROPP is metalized; and f) a furocoumarin conjugated with a light emitting  
8    photosensitizer, F-LEP.

9       The foregoing super-class of conjugated compounds can be used to treat a  
10   variety of diseases such as atherosclerosis, restenosis, cancer, cancer precursors, non-  
11   cancerous hyperproliferative diseases, psoriasis, macular degeneration, glaucoma, and  
12   certain viruses. These compounds are light activatable drugs which may or may not be  
13   photodynamically active (i.e. produce singlet oxygen and/or oxygen radicals to mediate  
14   cytotoxicity), but will be photoactive (i.e. exhibit photochemical cross-linking with  
15   DNA or RNA or the production of monoadducts of the compound therewith) to  
16   modulate the metabolic activity of cells. More specifically, these novel photoactive  
17   compounds will retain the ability of the ROPP or LEP to localize to a greater extent in  
18   the target tissue and the ability of the furocoumarin (such as psoralen) to intercalate  
19   into target tissue DNA and form cross-linked and/or monoadducts adducts upon the  
20   addition of light energy.

21       Previous studies indicate that utilizing a cationic ROPP or LEP to synthesize a  
22   CF-ROPP or CF-LEP facilitates the intercalation of the compound into target cell  
23   DNA. Once the F-ROPP or CF-ROPP is localized in target cells, light activation can  
24   be used therapeutically and/or diagnostically. The use of these novel compounds for

1 the detection and/or treatment and the prevention of restenosis and intimal hyperplasia  
2 following cardiac transplantation surgery (or AV shunt procedures such as dialysis) is  
3 an exemplary application which is discussed in particular detail to teach and illustrate a  
4 use for the invention, but it should be kept in mind that such an application is  
5 illustrative and should not be construed as a limitation of this invention.

6 For example, another application for the photosensitizer compounds described  
7 herein is the light activated treatment of a target tissue which does not selectively  
8 concentrate either ROPPs or furocoumarins. An F-ROPP, selected as described below  
9 from the super-class of compounds described above, can be administered systemically  
10 to a biological organism, which organism could be an animal, a plant or even a single  
11 cell or a polynucleic acid fragment. Following systemic administration of the F-ROPP,  
12 and while the F-ROPP is present in the animal's serum, a light source operating at a  
13 strong absorption wavelength of the furocoumarin component of the F-ROPP, is  
14 directed toward the volume of target tissue in which high concentrations of the F-  
15 ROPP are desired. The selection of the particular furocoumarin used in the F-ROPP is  
16 preferably a species which creates mono-adducts with polynucleic acids when activated  
17 with UV or short wavelength visible light. By administering the activating light to the  
18 target tissue, mono-adducts of F-ROPPs with DNA and RNA are formed. Increasing  
19 the intensity of the activating light delivered to the target tissue increases the DNA-  
20 bound F-ROPP therein. When the F-ROPP reaches the desired concentration in the  
21 target tissue, a longer wavelength of light which activates the ROPP portion of the F-  
22 ROPP may be used to photoactivate the cell bound F-ROPP in the target tissues to  
23 selectively destroy or modify the target tissue. In effect, the F-ROPP creates a light-  
24 induced selectivity of the F-ROPP for binding to the target tissue because only the

1 target tissue is illuminated with the shorter wavelength of light thereby causing  
2 covalent bonding of F-ROPP only in the DNA/RNA of the target tissue.

3 While particular embodiments of the present invention have been illustrated and  
4 described, it would be obvious to those skilled in the art that various other changes and  
5 modifications can be made without departing from the spirit and scope of the  
6 invention. It is therefore intended to cover in the impending claims all such changes  
7 and modifications that are within the scope of this invention.

8

9

10

11

1

**CLAIMS**

2       1. Photoactive compounds comprising a functional furocoumarin conjugated  
3       with a photosensitive benzochlorin compound.

4       2. The photoactive compounds of Claim 1 wherein the photosensitive  
5       benzochlorin compound is cationic.

6       3. The photoactive compound of Claim 1 wherein said photosensitive compound  
7       comprises a metal coordinated to a benzochlorin molecule.

8       4. The photoactive compound of Claim 3 wherein the metal is selected from the  
9       group consisting of copper, aluminum, tin, zinc, gadolinium, manganese, magnesium or  
10      iron.

11      5. The photoactive compounds of Claim 1 wherein said functional furocoumarin  
12      comprises a psoralen.

13      6. A photoactive compound having the structure R-R<sup>1</sup> wherein R comprises a  
14      furocoumarin and wherein R<sup>1</sup> is a reactive oxygen-producing benzochlorin compound.

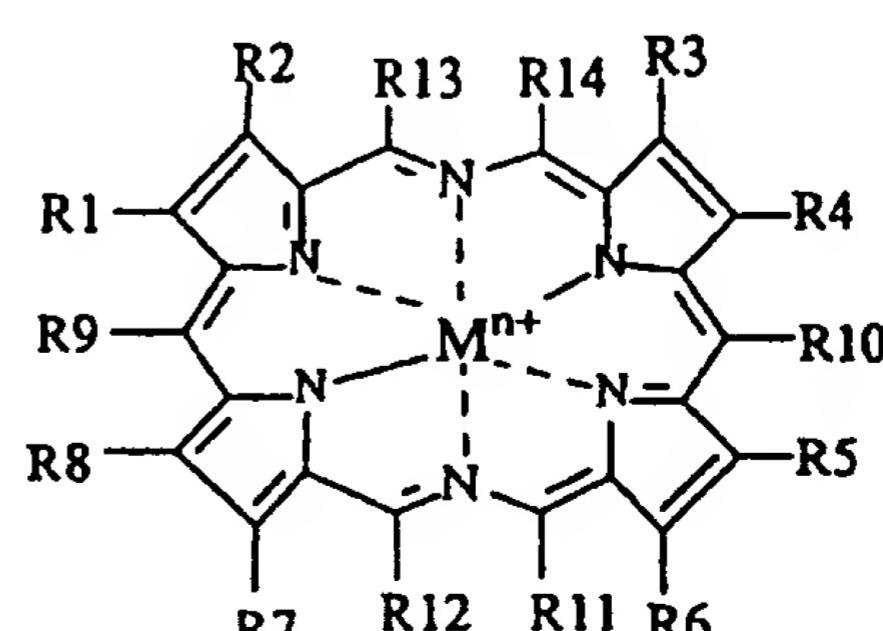
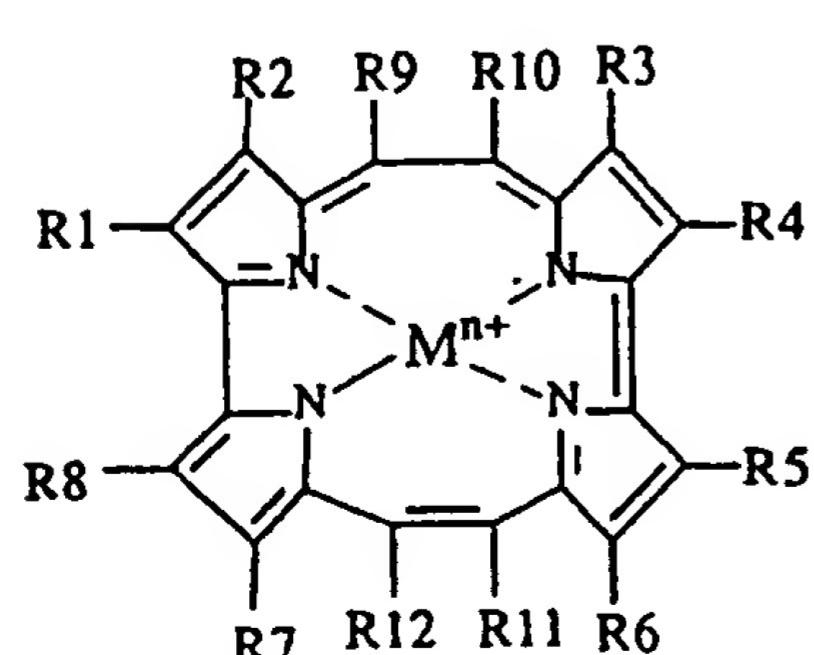
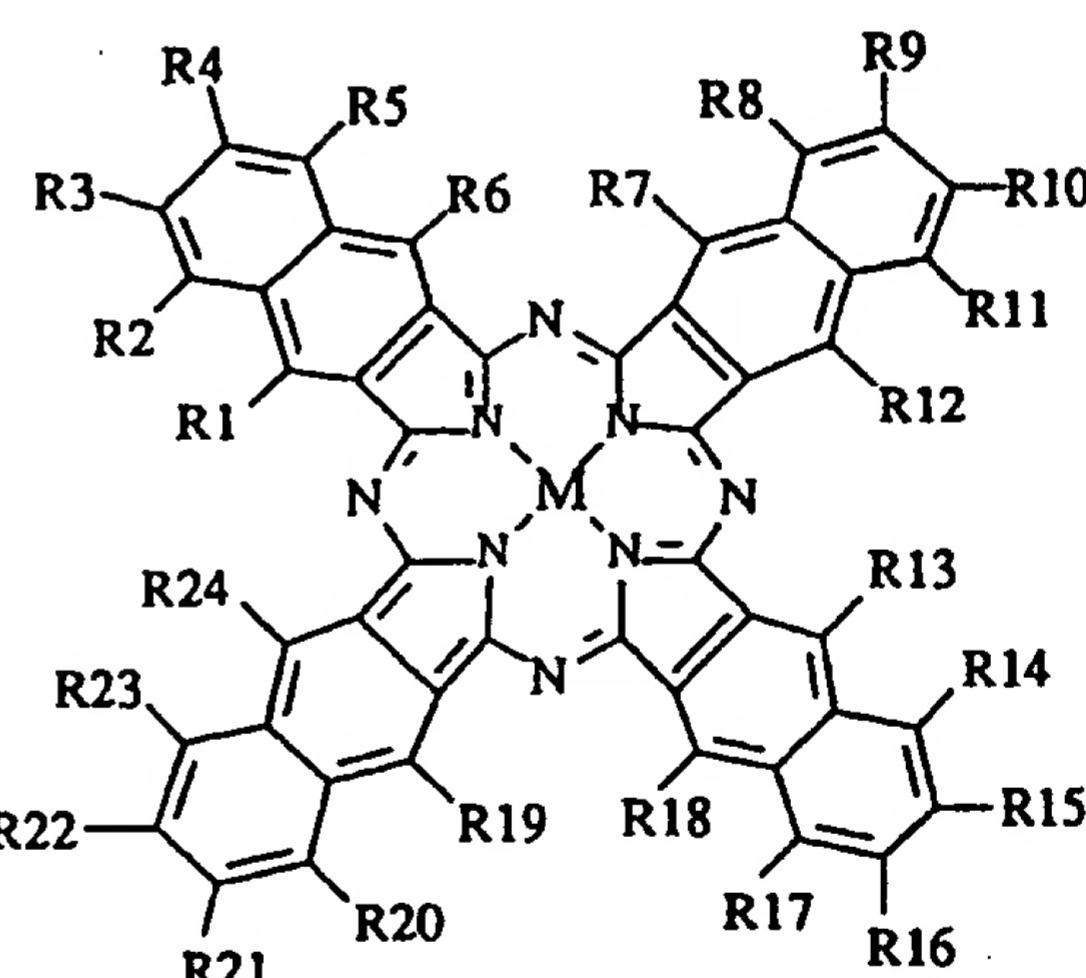
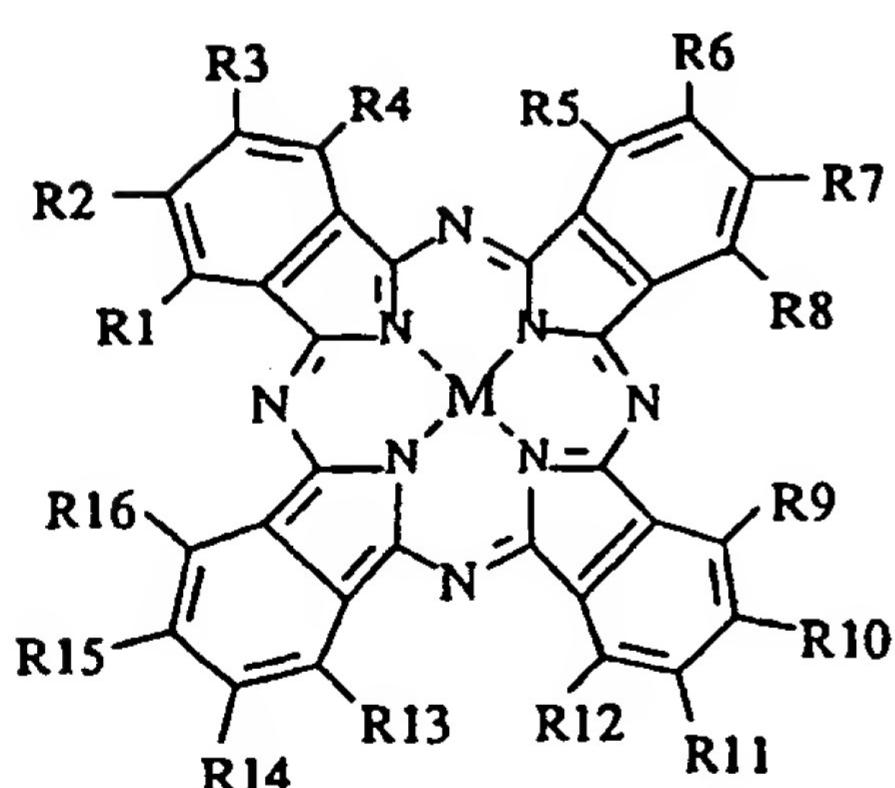
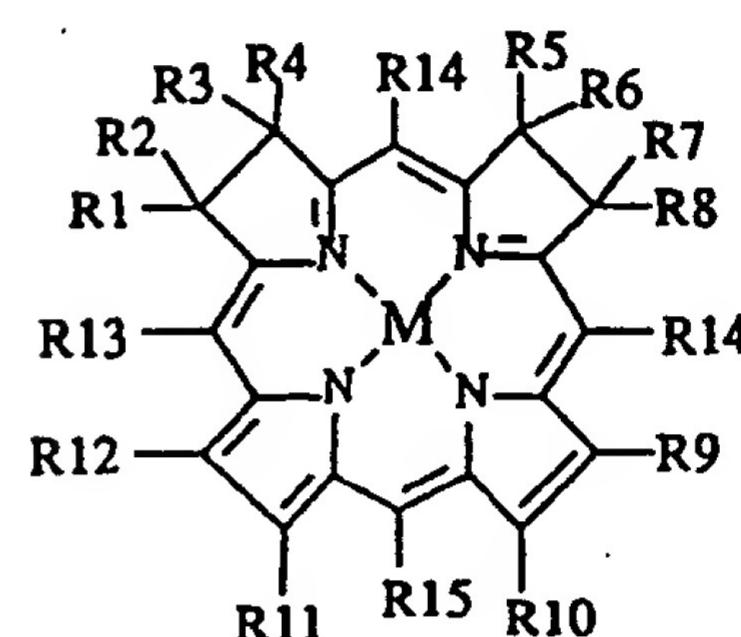
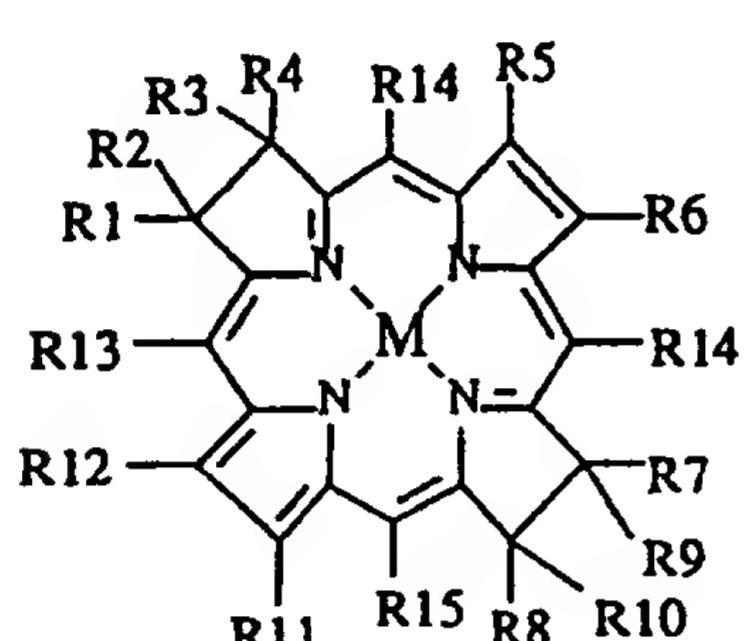
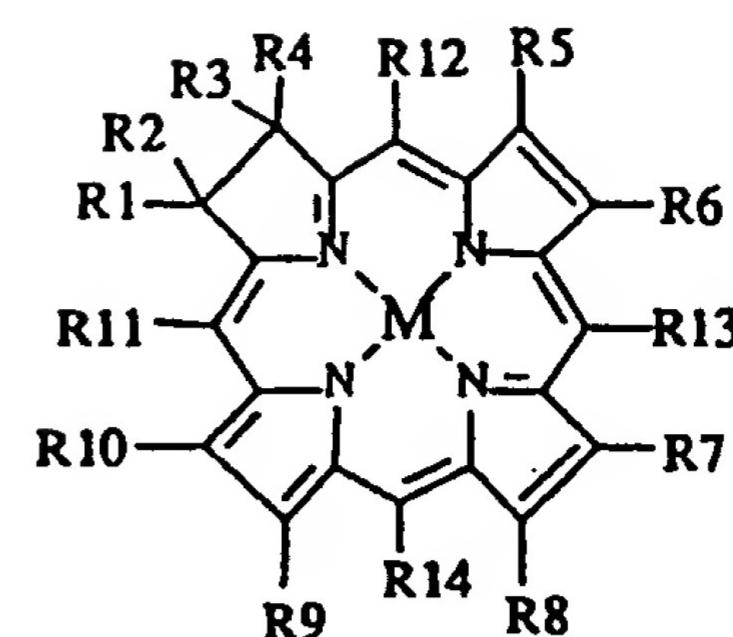
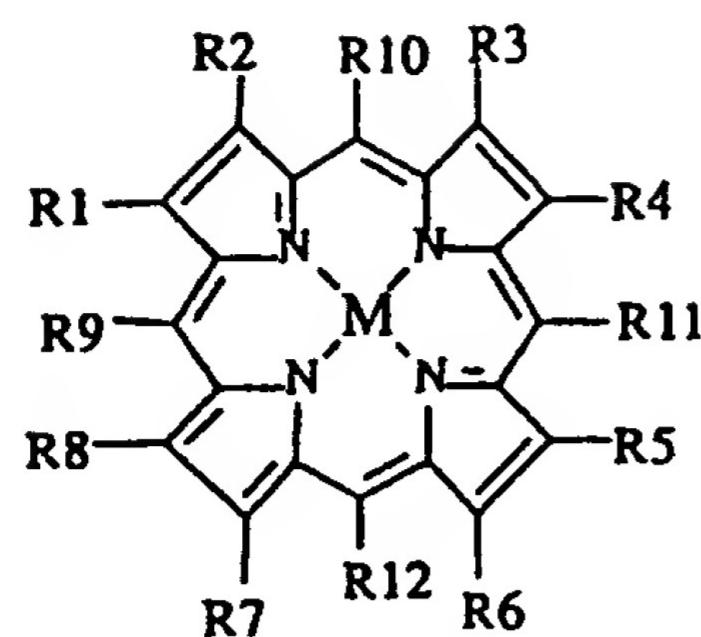
15      7. A photoactive compound in accordance Claim 9 wherein R<sup>1</sup> is a light-emitting  
16      benzochlorin compound.

17      8. A photoactive compound in accordance Claim 9 wherein said furocoumarin is  
18      selected from the group consisting of compounds comprising isopsoralen,  
19      pseudopsoralen, pseudoisopsoralen, allopsoralen and pseudoallopsoralen; or  
20      derivatives thereof.

21      9. A photoactive composition for treating diseased target tissue cells within an  
22      organism, said photoactive composition having the form R-R' wherein R is a  
23      photoactivatable furocoumarin compound which covalently bonds to target tissue cells  
24      only when the furocoumarin compound is photoactivated with light having a first

1 wavelength, and R' is a photosensitive benzochlorin compound which interferes with  
2 normal cellular activity within the diseased target tissue only when photoactivated with  
3 light having a second wavelength, which second wavelength is different from said first  
4 wavelength.

5        10. Photoactive compounds comprising a functional furocoumarin conjugated  
6 with a photosensitive pyrrole-derived macrocyclic compound.



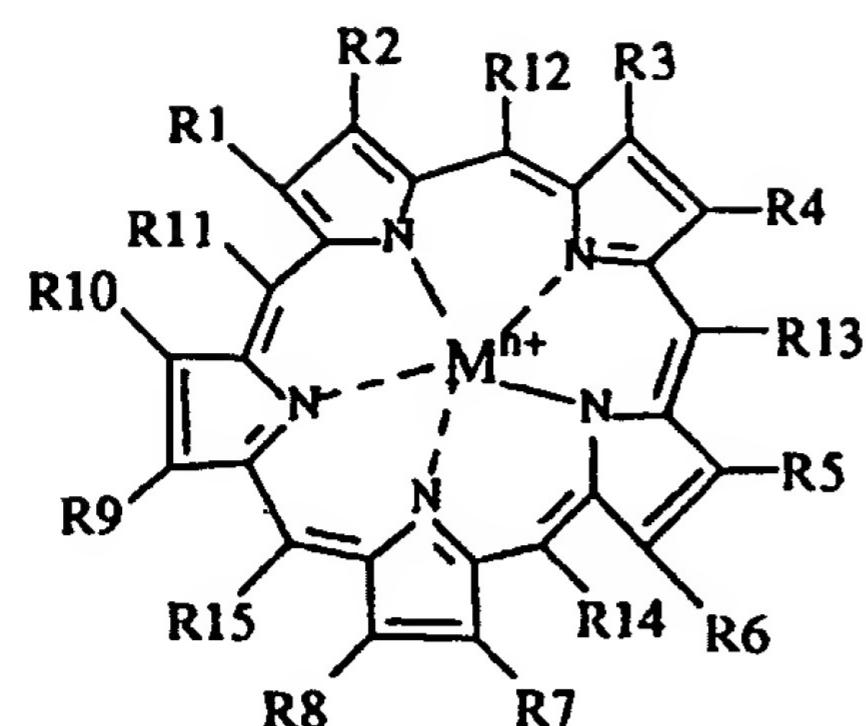


FIG.9

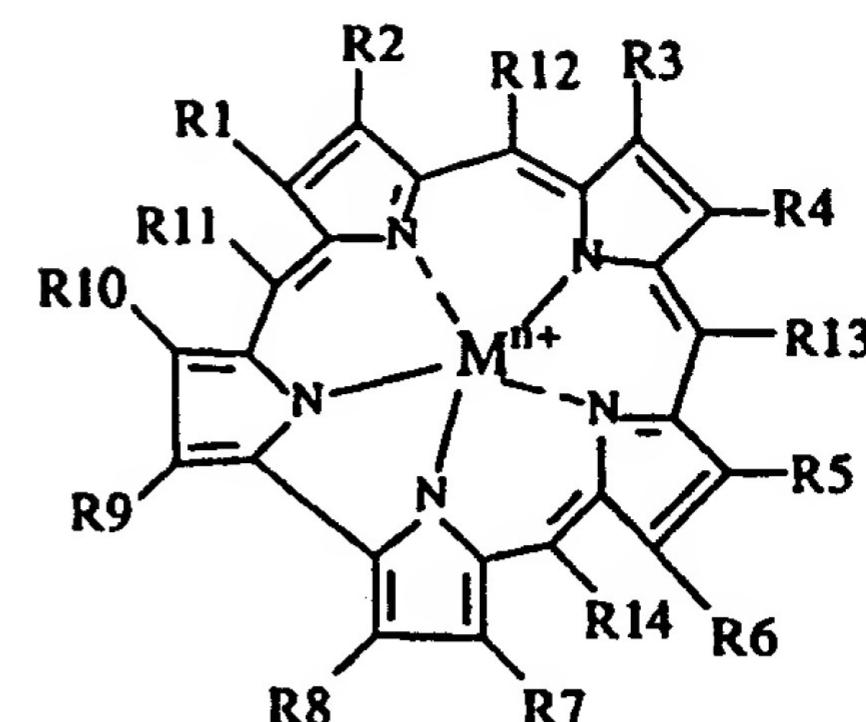


FIG.10

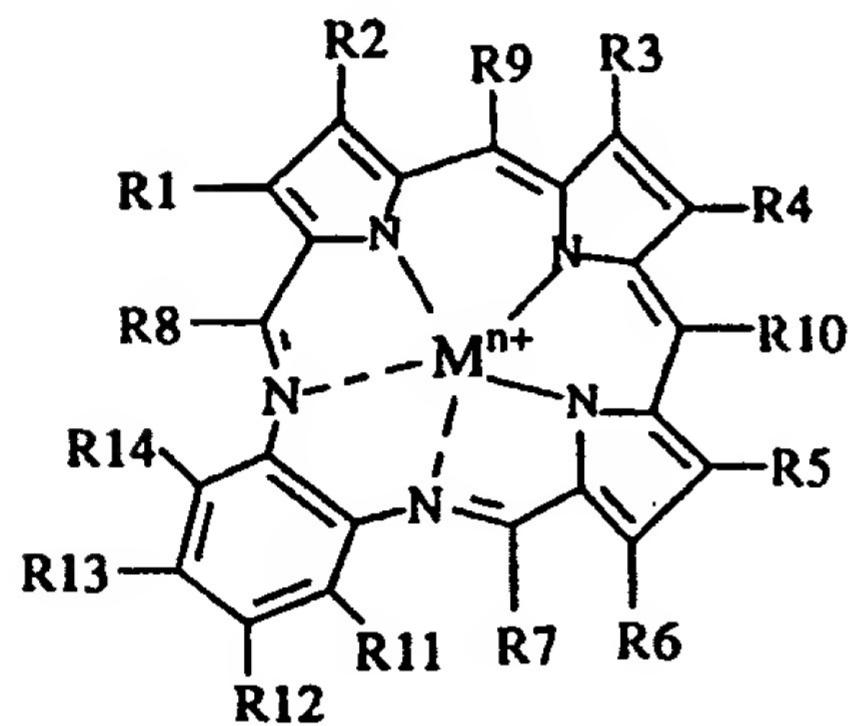


FIG.11

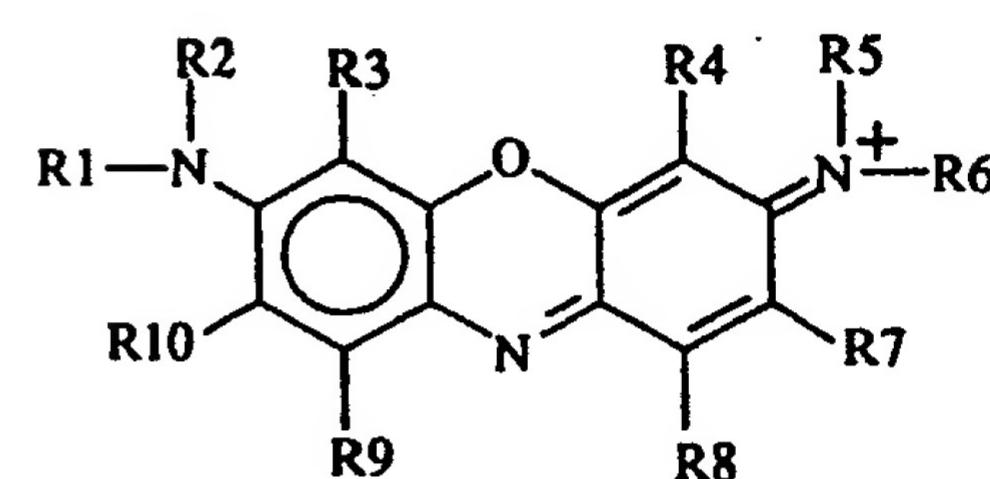


FIG.12

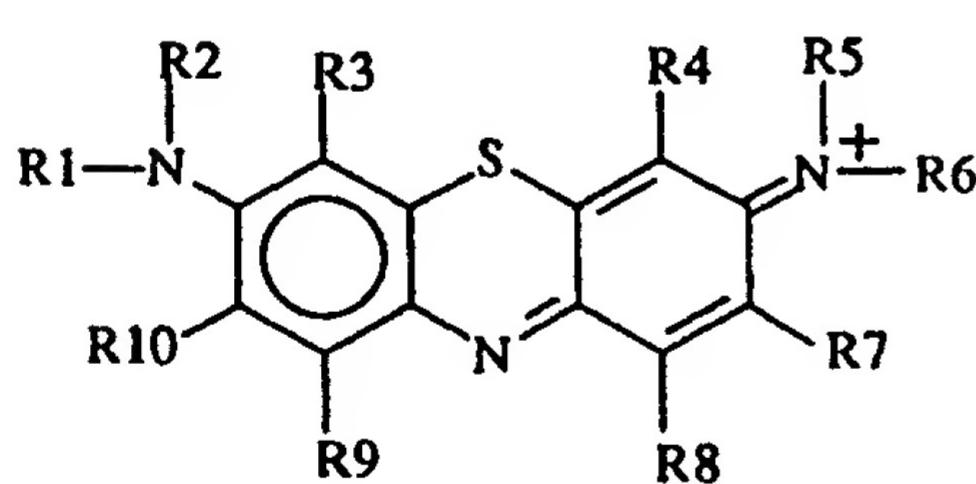


FIG.13

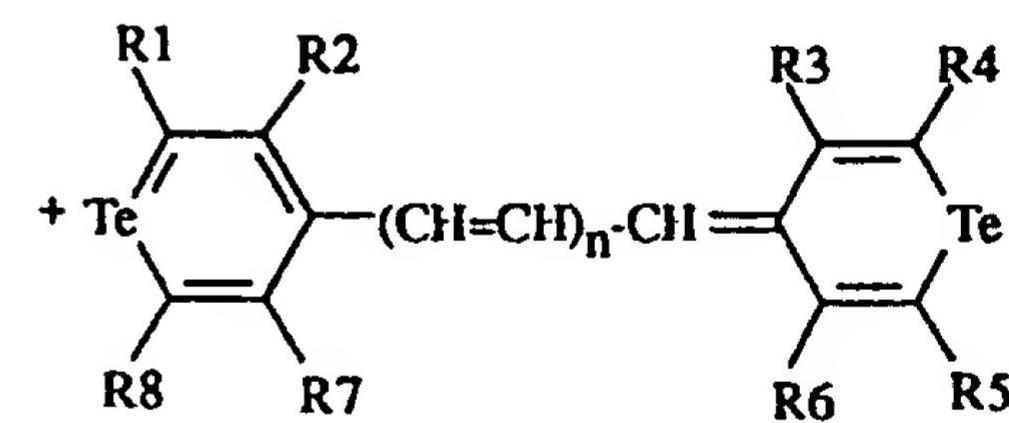


FIG.14

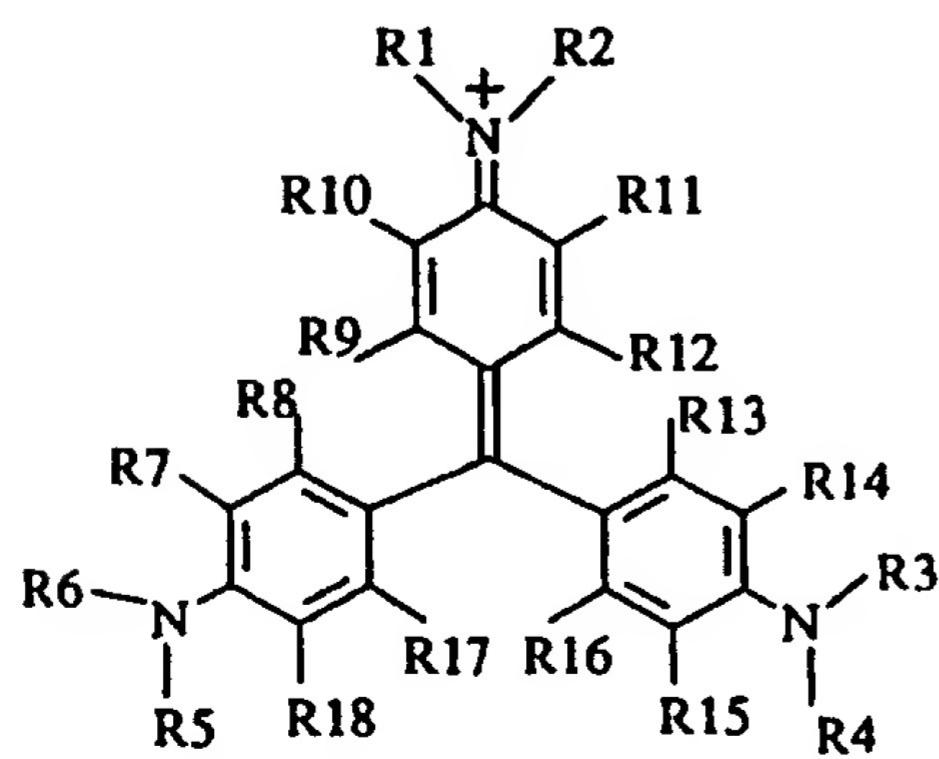


FIG.15

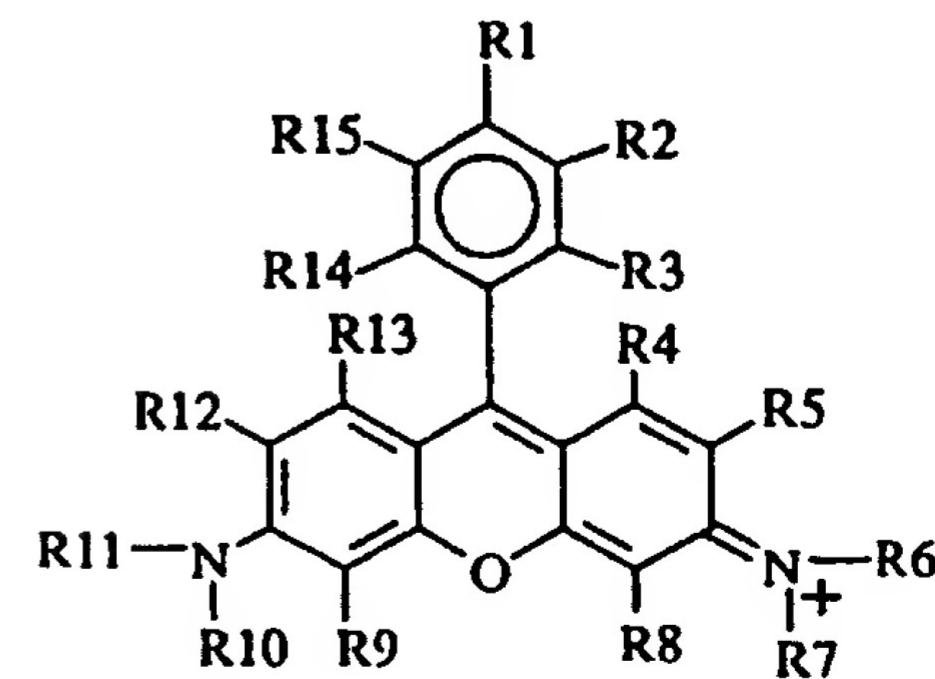
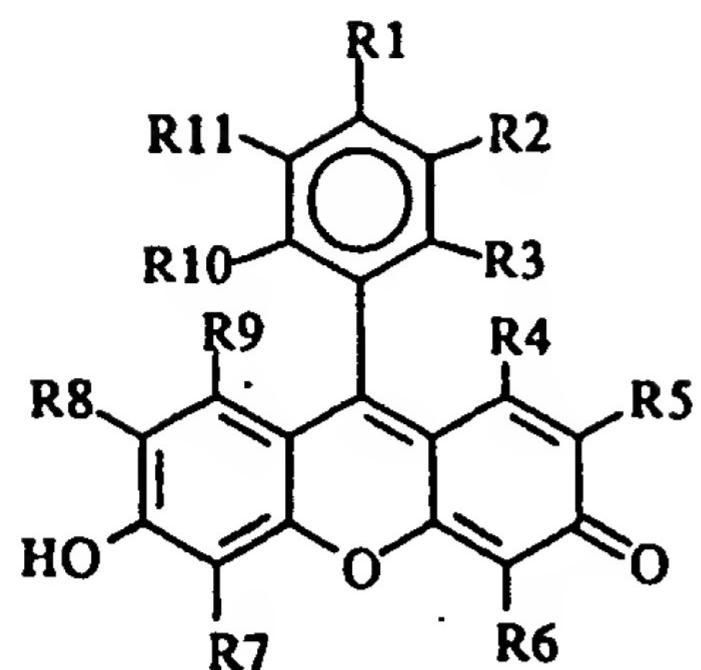
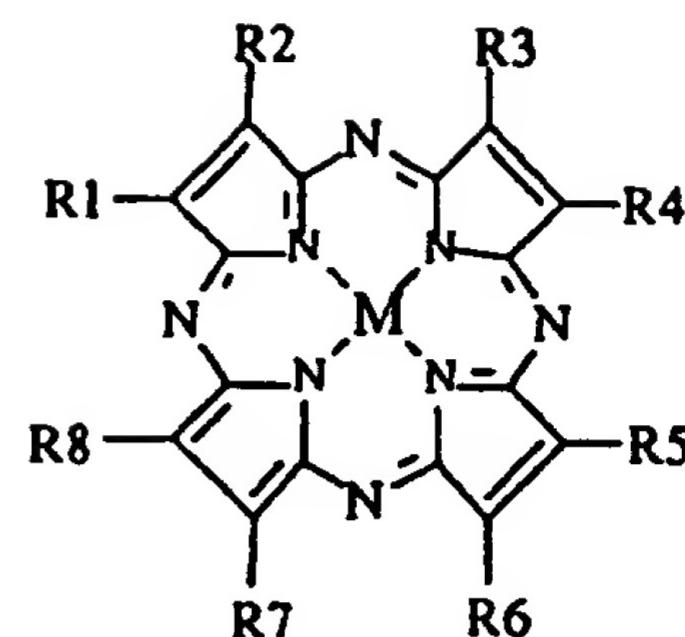
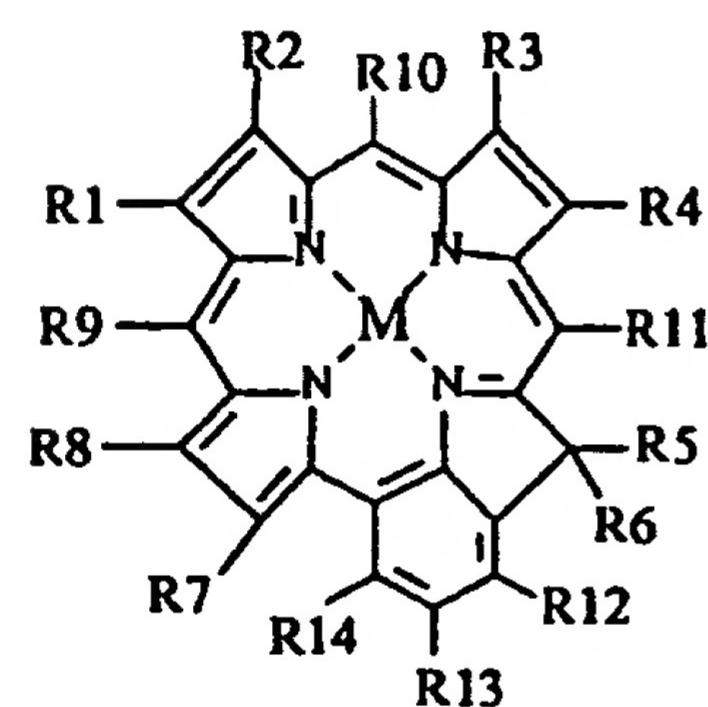
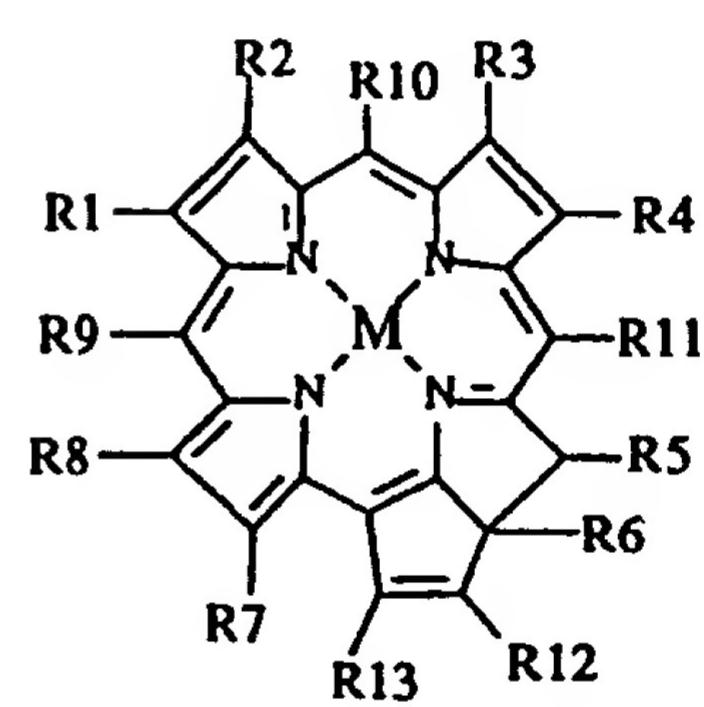
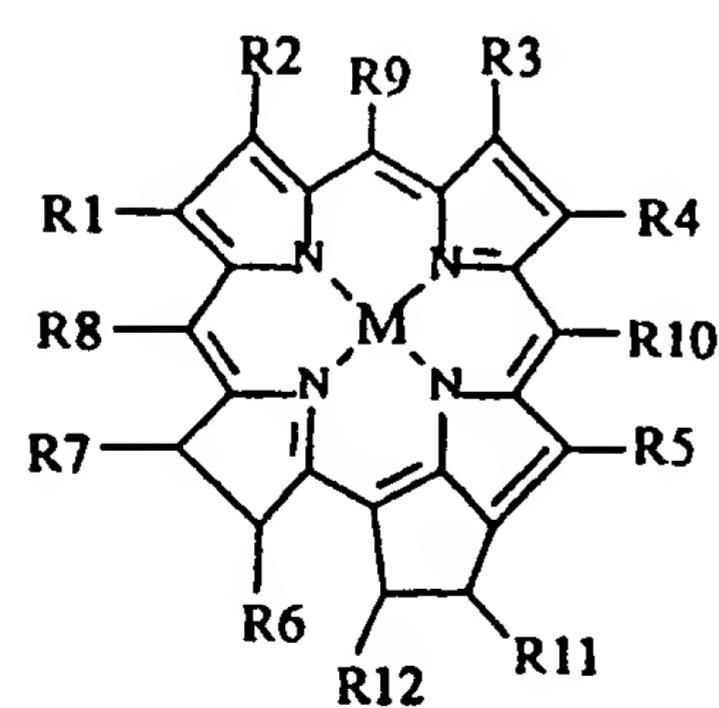
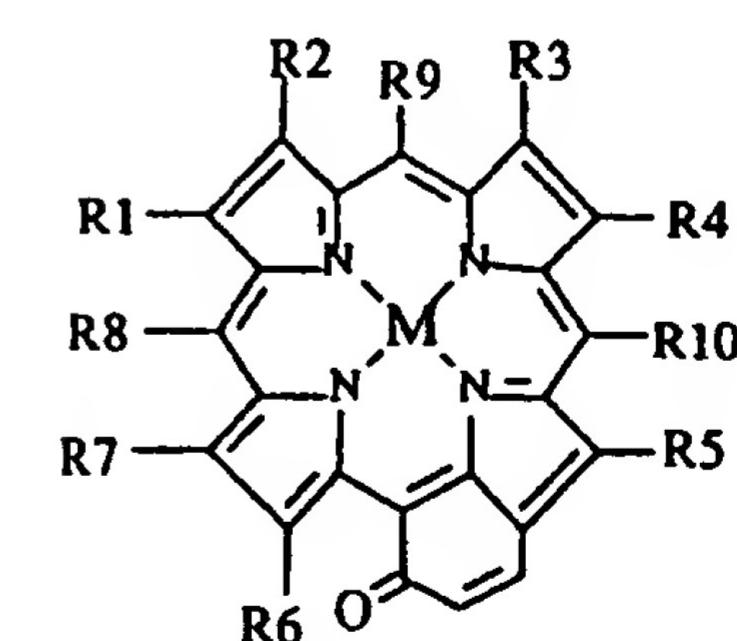


FIG.16

**FIG.17****FIG.18****FIG.19****FIG.20****FIG.21****FIG.22**

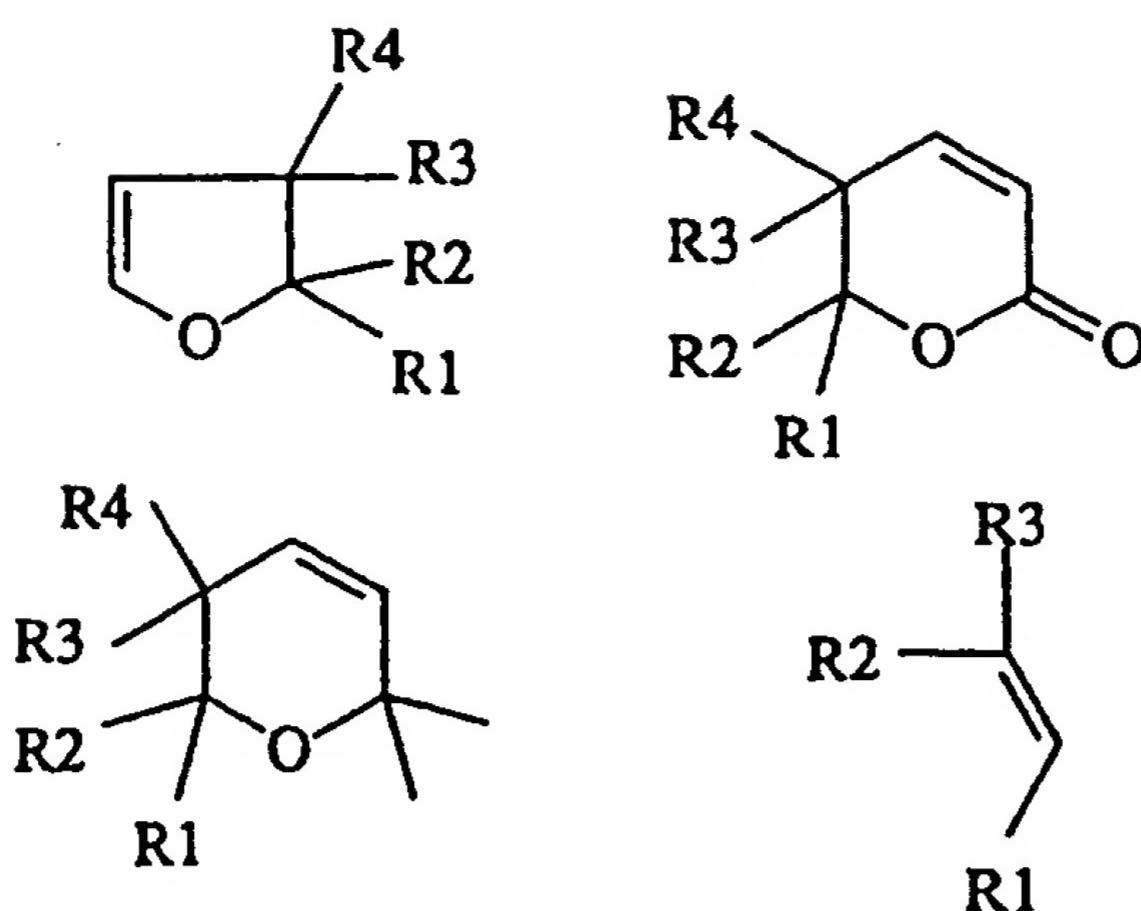


FIG.23

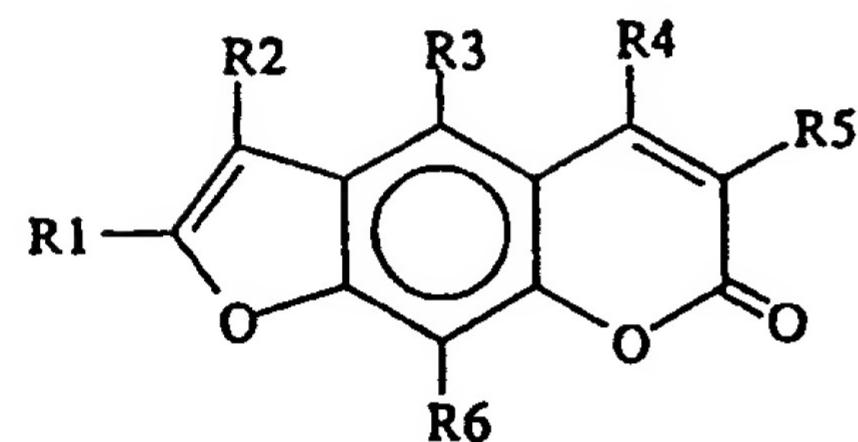


FIG.24

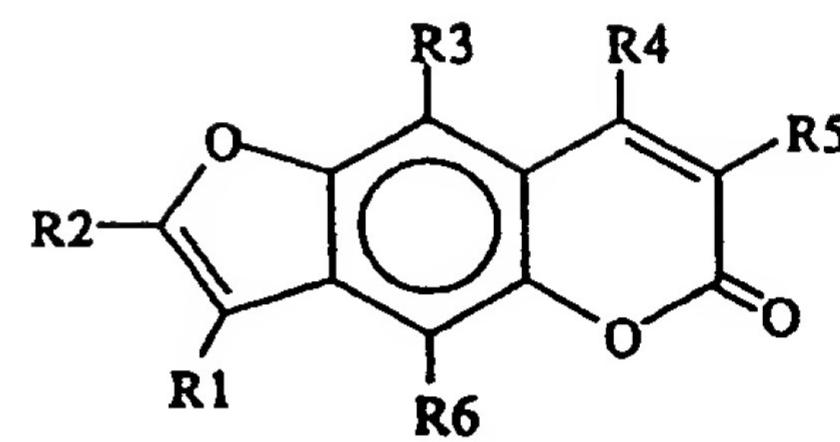


FIG.25

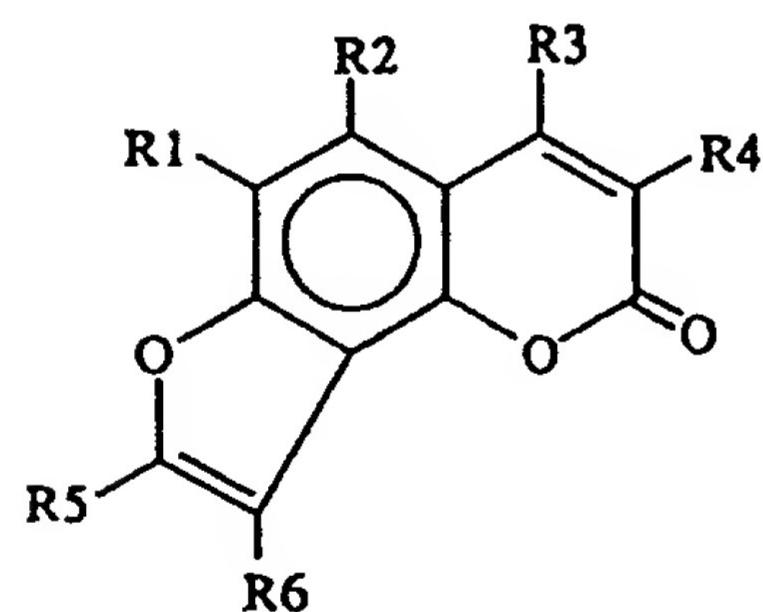


FIG.26

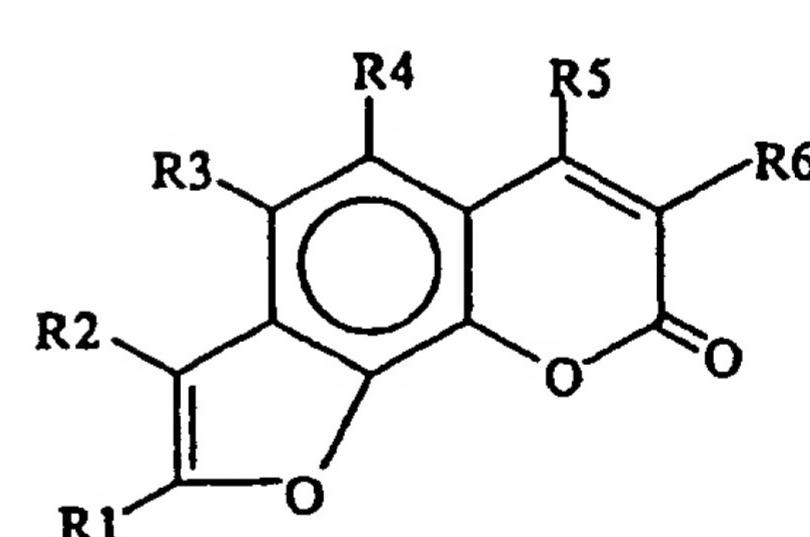


FIG.27

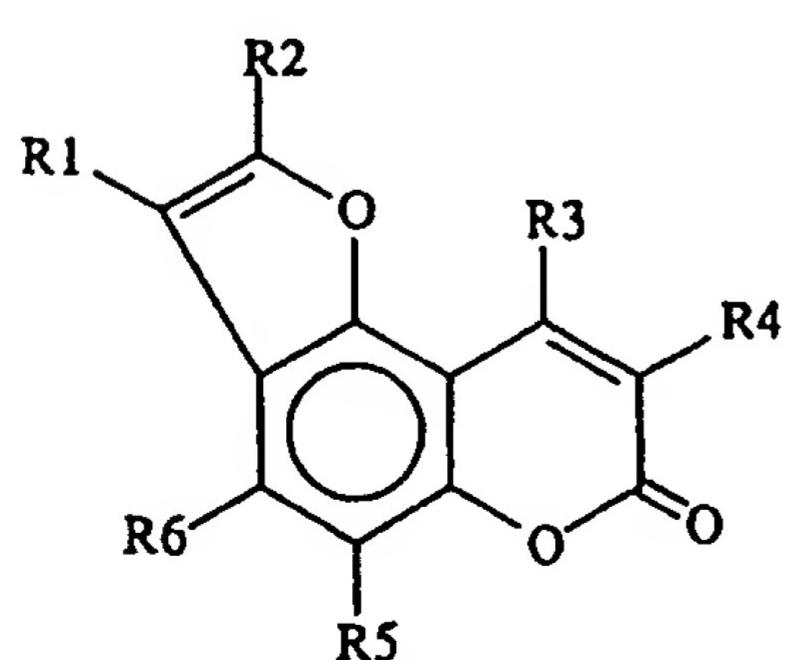


FIG.28

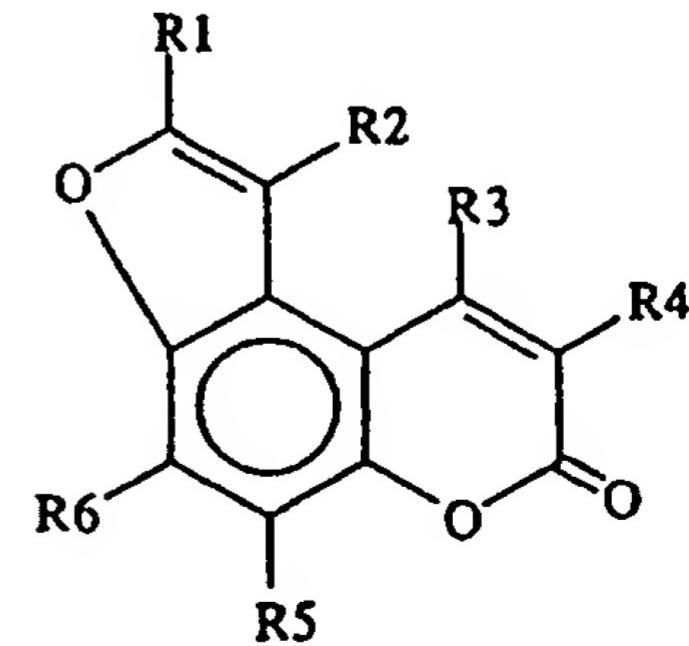


FIG.29

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/12128

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 309/38; C07D 487/22

US CL :549/387; 540/ 145

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 549/387; 540/145

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS SEARCH

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A 5,356,929 (HEINDEL et al) 18 October 1994, See columns 1 and 2.	1-10
Y	US, A, 5,286,474 (GUST et al.) 15 February 1994, See entire document.	1-10
A, E	US, A, 5,539,100 (WASIELEWSKI et al.) 23 July 1996, See entire document.	1-10

Further documents are listed in the continuation of Box C.

See patent family annex.

Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"O" document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

03 OCTOBER 1996

Date of mailing of the international search report

06 NOV 1996

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